

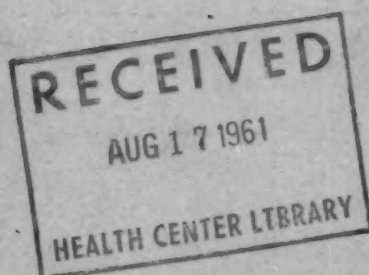
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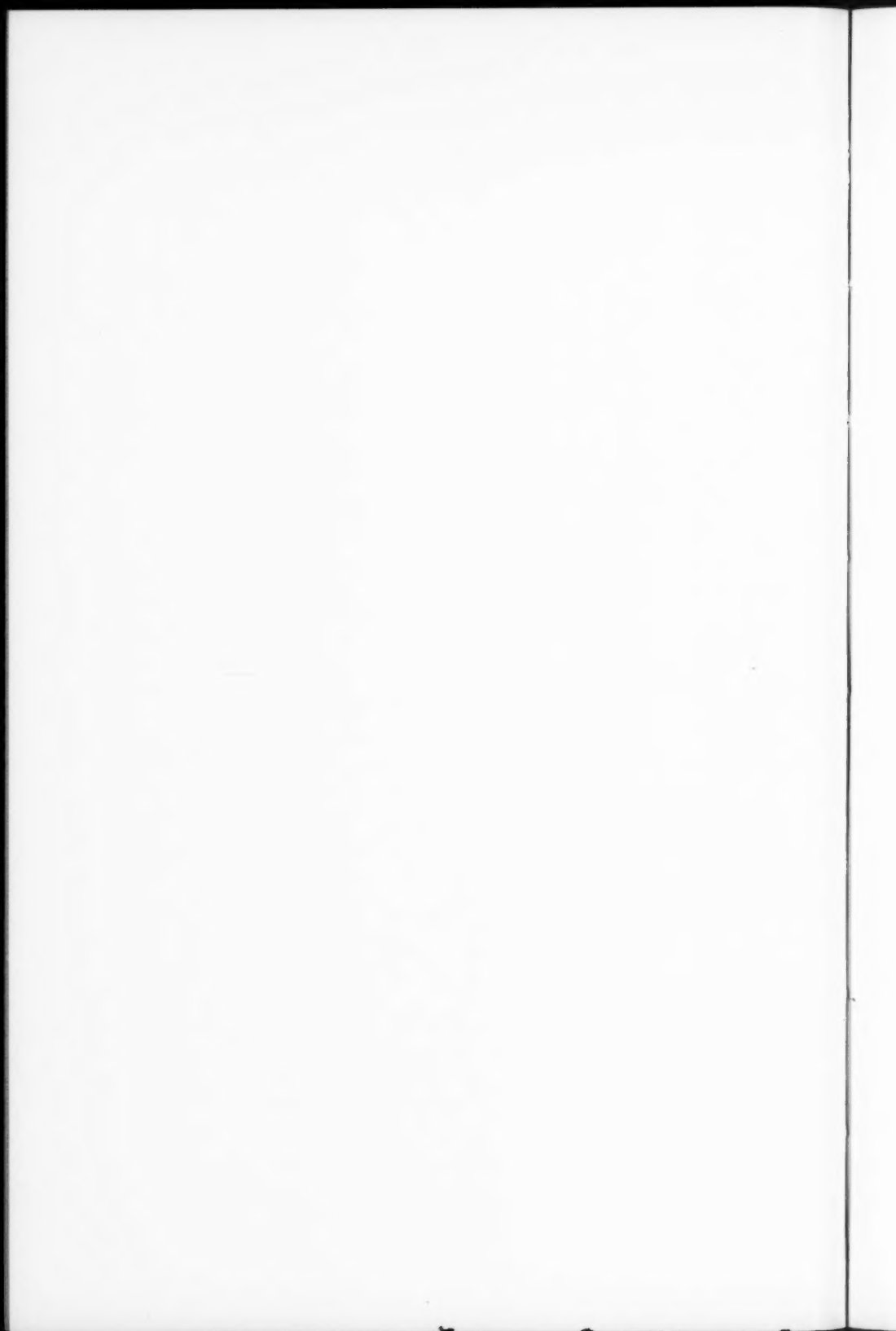
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XXV

PROSPER MENIÈRE

THE CENTENARY OF AN EPONYM

HILTON H. STOTHERS, M.D.

NEW YORK, N. Y.

From time to time a scientific report appears which, by its impact on contemporary beliefs and its contribution to the advancement of knowledge, inevitably becomes a classic. Such an occurrence took place on January 8, 1861, when Prosper Menière read before the Paris Academy of Medicine his paper "sur une forme du surdit  grave d pendant d'une l sion de l'oreille interne."¹ He followed this presentation with a series of five articles²⁻⁶ on the same subject which were published in the Gazette M dicale de Paris during 1861, the final year of his life. Describing in these reports an affection characterized by paroxysmal crises of vertigo, deafness and tinnitus, Meni re was the first to ascribe the cause of the disorder to the internal ear. This event made Meni re known through the disease named after him. Furthermore, it generated a century of controversy concerning the identity and significance of what he had defined. In observing the end of that century, it is fitting to review the life of this physician, the background of his discovery, and the career of his famous eponym.

Meni re, the third of four children of a small merchant, was born at Angers, France, on June 18, 1799. He obtained his early education in his native city, and began his medical learning in the Lyc e there. In 1819 he went to Paris to continue his studies in medicine. He was awarded a gold medal in 1826, during the course of a brilliant student career, and obtained his medical degree in 1828 with a thesis⁷ on the

Read before the New York Academy of Medicine, Section on Otolaryngology, February 15, 1961.

state of public health in the third quarter of the year 1826. He was serving as clinical assistant to Dupuytren, the great surgeon of the Hôtel-Dieu, during the time of the bloody political revolution in July and August of 1830, when Charles X abdicated and Louis Philippe ascended the throne. The many wounded admitted to the hospital wards afforded Menière a unique opportunity for observation. He wrote a vivid account⁸ of his experience, and Dupuytren is said to have freely used this record for his treatise on war injuries.

In 1832 Menière was appointed assistant professor on the Paris faculty of medicine, but his career was interrupted in an unexpected manner. On the recommendation of his friend Orfila, medico-legal expert and dean of the University, Menière was nominated by the government of Louis Philippe to verify the suspected pregnancy of the Duchesse de Berry, daughter of the King of Naples and widow of the son of deposed Charles X. Her husband had been murdered in 1820, seven months before the birth of his son, who became generally known as the "miracle child," and to his hopeful partisans, as Henry V of France. The ambitious duchess had returned from exile and landed near Marseilles, in April 1832, in an attempt to secure the throne for her 11-year-old son. Her followers were defeated by the government forces and she herself was captured and imprisoned in the castle of Blays. Menière confirmed the pregnancy of the prisoner, and soon afterward she gave birth to a daughter conceived in a secret marriage to an Italian nobleman. The revelation of these facts deprived the duchess of the sympathy of her supporters and lost for her little son, the Duc de Bordeaux, any chance of becoming king of France. Meanwhile, Menière had gained her confidence and friendship and upon her release, she asked him to accompany her to Sicily. After a six months' tour of Italy, Menière returned to Paris to find that the incident had gained for him favorable notice.

Menière was made a Fellow of the University in 1834, and for a short time lectured on hygiene and acted as assistant to Professor Auguste Chomel. In 1835 he was sent on a government mission to Southern France to combat an epidemic of cholera and for his services was made a Chevalier of the Legion of Honor. Later he took over the chair of obstetrics, temporarily replacing Paul DuBois. In 1837 Menière submitted an excellent thesis⁹ on clothes and cosmetics but failed to obtain the professorship of medicine and hygiene vacated by Chomel. In the following year, Itard, physician-in-chief of the Imperial Institute for Deaf-mutes, died and Menière was elected to replace him. Thereafter his professional work lay almost entirely in the field of otology.

In 1838, Menière married Mlle. Becquerel, a member of the distinguished family of scientists, which included Antoine Becquerel, the discoverer of radioactivity. Menière's only son, Emile (1839-1905), became a noted otologist and later occupied his father's former position at the Institute for Deaf-mutes. Prosper Menière became one of the foremost physicians of France, while his lectures and clinics attracted many students and visitors. Among the latter, in 1861, was the young Adam Politzer of Hungary, who, fifty years later, was proud to record their personal meeting.¹⁰ After spending his entire professional career in Paris, Menière died of influenzal pneumonia on February 7, 1862 and was buried in the cemetery of Montparnasse.

Early in life, Menière had acquired a deep knowledge of anatomy, surgery, and medicine, and endowed with a remarkable memory and writing ability, he produced many contributions to medical literature over a period of thirty years. The various subjects he covered until the appearance of his first paper on otology in 1841 reflected his changing interests in medical science, especially obstetrics and gynecology. His published works are too numerous to mention individually, but the more important ones are listed in the present bibliography. All of his scientific writings exhibit his power of accurate observation and clear reasoning. A random example is his article¹¹ on emphysema from diverse causes, which allegedly¹² contains the first mention of emphysema of the upper eye-lid as a sign of fracture of the lacrymal bone or inner wall of the orbit. The reader is constantly impressed with Menière's diligent research for the seat of disease and with his attempt to correlate clinical signs with anatomical findings. The exercise of this basic principle, proclaimed by Morgagni a century earlier, was to stand Menière in good stead at the moment of his famous discovery.

It has been observed that the successful pursuit of bilateral careers, one in science and the other in the arts, has been achieved by few men; for most men, such careers are consecutive rather than concurrent accomplishments. In Menière's case, his entire career was distinguished by a truly remarkable blend of medicine and literature. His literary works include his diary of anecdotes,¹³ written during the imprisonment of the Duchesse de Berry, and his "Journal"¹⁴ of reminiscences of interesting events and conversations of great men of the Second Empire whom he had known. Both of these books were published posthumously by his son, as was also his "Consultations de Mme. de Sévigné";¹⁵ the latter work was a compilation of the generous and often unorthodox medical advice of this clever and witty letter-writer of 17th century France. Menière's inclinations, however, were



Fig. 1.—Prosper Menière in 1833. Portrait by Bodinier.

more specially oriented toward the study of poetry and the medical history of antiquity.¹⁶ His profound knowledge of the Greek and Latin classics was responsible for two scholarly volumes, one on medical studies of the Latin poets and the other on Cicero as a physician. In the first volume,¹⁷ Menière delineated the medical ideas and practices of the Roman Republic and early Empire, as portrayed by such writers as Virgil, Horace, Lucretius, Ovid, and Juvenal. In the second,¹⁸ he exposed Cicero's vast knowledge of medical lore. Menière's ambition to publish an analogous study of the Greece of Homer, Sappho, and Sophocles was not fulfilled before his death. His interest in poetry led him, at least once, to a modest personal effort, which

Chereau¹⁹ considered worthy of inclusion in his anthology of poems by physicians of France.

Menière was fortunate in beginning his career under most favorable auspices. After studying under the leading clinicians of Paris, he won the close and lasting friendship of the influential Orfila, and this relationship opened many important doors for him. Since he was a cultured man of character and great personal charm, Menière soon became a favorite in the highest scientific, literary, and governmental circles. After a busy day with his extensive medical practice, his teaching, and other professional activities, he delighted in spending an evening at the home of friends such as Orfila, Jules Janin, the literary critic, and Pasquier, the former chancellor of state in Napoleon's cabinet. It was in this circle that Menière became an intimate of such well-known figures as Balzac, Sainte-Beuve, and Victor Hugo.

Menière's versatility manifested itself in many other ways. He was an amateur archeologist of some standing, and his deep interest in botany admitted him to membership in the ranking botanical societies of France. The quality and clarity of his literary style created demands on him for numerous essays, critical reviews, and accurate reports of the proceedings of several medical clinics. He even acquired repute for his graceful eulogies of deceased colleagues!

Above all, Menière's claim to fame was the demonstration that a particular syndrome of tinnitus, vertigo, and loss of hearing, previously regarded as evidence of a cerebral lesion, is caused by disturbed labyrinthine function. To appreciate the importance of this discovery, it is necessary to examine briefly the state of otological knowledge of his time and of the period prior to it.

Vesalius' knowledge of the middle and internal ears was quite sketchy. In 1561, Fallopius, his successor in the chair of anatomy at Padua, gave a fairly accurate description of the osseous structures of the internal ear. He named the labyrinth, and described the cochlea and the vestibule, and is accorded priority in the discovery of the semicircular canals. A contemporary, Eustachius, rediscovered the tube bearing his name and gave a more accurate description of the cochlea. A century later, Duverney published what is generally regarded as the first book devoted to otology, in which he indicated that he knew of the membranous labyrinth. Valsalva further investigated the internal ear and concerned himself with the correlation between physiology and anatomy. In the 18th century, the concept of the ear solely as an organ of hearing spread rapidly, after Cotugno

proved the existence of fluid within the labyrinth. The study of macroscopic aural anatomy culminated in the important discoveries of the intralabyrinthine structures by Scarpa. All of these anatomists regarded the semicircular canals strictly as factors in the function of hearing, and none suspected the dual function of the labyrinth. Vertigo was explained on the basis of gastric disturbances.

Knowledge of the physiology of audition, and especially of vestibular function, developed very slowly during the 19th century. Purkinje, in 1820, made the first careful studies of vertigo, but his investigations dealt chiefly with the objective ocular manifestations of rotation of the body. In 1828, Flourens experimented on pigeons by dividing the semicircular canals. He thereby demonstrated the existence of true labyrinthine vertigo; but he did not recognize it as such, since he was confused by the current belief in the role of the cerebellum as the mediator of equilibratory function. Thus, vertigo and vestibular disturbances had both been investigated as separate entities without relation to each other. It seems that until Menière's work appeared, no one associated the characteristic dysfunction caused by vestibular experiments on animals with clinical vertigo as experienced by man. The differentiation of labyrinthine vertigo as a specific disorder is a brilliant example of the application of the results of physiological experiment to the explanation of a disease.

Menière was not unprepared for his great discovery. His predecessor as chief at the Institute for Deaf-mutes was the French pioneer otologist, Itard, whose excellent text-book²⁰ on diseases of the ear did much to establish the specialty on a scientific level. The work of the German otologist, Kramer, was also well known to Menière, who in 1848, had translated his notable book into French from an English translation of the original. Menière's edition²¹ was not simply a translation but actually a revision with many footnotes and critical comments, including two additional chapters epitomizing his own views on the internal ear. It was in this work (page 397) that Menière first mentioned the famous autopsy to which he later alluded in 1861. As a contemporary of Toynbee of London, Wilde of Dublin, and Von Tröltsch of Wursburg, Menière was one of a generation of able clinicians well trained in anatomy and active in the most dynamic period of otological history. These were the men who, in the middle of the 19th century, effectively developed the specialty into a reputable science. With his extensive knowledge of anatomy and his active interest in the recent discoveries in physiology, Menière was able to achieve success when the opportunity presented itself. As Pasteur stated, "Chance favors only the prepared mind."

Menière had been speculating for a long time before 1861 about the clinical entity known thereafter by his name. He believed that it was of labyrinthine origin and was not apoplectiform cerebral congestion, the then current diagnosis, and was not related to epilepsy, as commonly believed. According to him, the symptoms included sudden attacks of vertigo associated with nausea and vomiting recurring for weeks, and perhaps months or years, but leaving the patient in perfect health between attacks, except for some deafness. Menière stressed particularly the loss of hearing, noting that it might be bilateral though more often unilateral, that it was of nerve type but involved the low frequencies more than the high, and was accompanied by tinnitus in the affected ear. He observed that the violent symptoms of an attack had often been mistaken as evidence of a brain lesion, but that there was never any residual paralysis, and after the attack the patient was quite well.

In order to emphasize Menière's postulates, his own resumé (in translation) of his original paper is presented as follows:

1. An auditory apparatus, previously perfectly normal, may suddenly become the seat of functional disorders consisting of noises of a variable nature, continuous or intermittent, and these noises are soon accompanied by a greater or lesser impairment of hearing.
2. These functional disorders, which have their seat in the internal auditory apparatus, may give rise to attacks believed to be cerebral, such as vertigo, giddiness, uncertain gait, turning and falling; furthermore, these attacks are accompanied by nausea, vomiting, and a state of syncope.
3. The attacks, which occur intermittently, are soon followed by progressively severe deafness, and frequently there is sudden and complete loss of hearing.
4. There is every reason to believe that the essential lesion causing these functional disorders lies in the semicircular canals.

As evidence that these symptoms were of labyrinthine origin, Menière cited the case of a young girl, who after travelling on the top of a stage-coach during a cold night at the time of her menses, suddenly became completely deaf and experienced continual vertigo and vomiting. Five days later the girl died. The autopsy showed no suppurative of the middle ear and no alteration in the brain or spinal cord. The only abnormality that Menière did find was "the semicircular canals filled with a red plastic material, a sort of blood-tinged exudate of which scarcely any traces were observed in the vestibule,



Fig. 2.—Prosper Menière.

and of which none existed in the cochlea." Contrary to an oft-repeated assertion, Menière did not imply that this case proved that the syndrome he had described was due to labyrinthine hemorrhage. It is clear that he cited the case in order to prove that the labyrinth, and not the brain, was the source of the vertigo. The exudate which he found in the labyrinth could not in itself explain the cause of death, and whether the case was one of hemorrhage, possibly due to leukemia, will probably never be determined. Epidemic cerebrospinal meningitis with extension into the internal ear, in which the meningeal condition had been overlooked, has also been offered as an alternate explanation. The cause of death in this case still remains uncertain; therefore, Menière's interpretation of his findings has been unjustifiably questioned. There is no evidence that Menière believed hemorrhage into the labyrinth to be the cause of the group of symptoms he was describing, or that he intended to present this case as typifying

the pathologic basis of the specific disease he was studying. Menière's actual findings in his famous autopsy, his purpose in presenting the case twice, and the reason for the discrepancy in the two records 13 years apart has puzzled some authors and has stimulated much speculation. The subject has been discussed separately by M'Kenzie²² and Atkinson,²³ but it remained finally for Williams²⁴ to recognize and clarify the significance of Menière's reports. Recently, additional light has been cast on the controversy by Tarlé.²⁵

The concept of aural or labyrinthine vertigo, as interpreted by Menière, was promptly accepted by such eminent otologists as Politzer, Von Trölsch, and Brunner in Europe, and by Knapp in the United States. This new interpretation was also pursued by outstanding clinicians of the period, especially Trousseau in France and Albutt in England. The attention of the general profession to the disorder, however, was attracted chiefly by the interest and repeated lectures of the neuropathologists Charcot and Hughlings Jackson, among others. For investigators in the field of neurology, Menière's discovery was of momentous importance. Nevertheless, further physiological experimentation and additional clinical observation were required and labyrinthine vertigo was not really understood until Bárány, in the early 20th century, differentiated it more accurately from lesions in the cerebellum, from epilepsy, and from other causes of nystagmus.

Menière died too soon after the publication of his discovery to know what a voluminous literature directly followed the event; but a brilliant young Parisian confrere was to insure fame for him. Simon Duplay (1836-1924), who became a great surgeon of France, was also an active contributor to scientific reviews. In 1863, in the *Archives Générales de Médecine*, he furnished one of the earliest reports²⁶ on Menière's work, in which he accurately quoted Menière's findings. In 1872, in the same journal,²⁷ of which he was then editor, Duplay discussed the subject more fully and suggested that the condition be designated "maladie de Menière"; this marked the first appearance of the eponym in the medical literature.

In 1875, there appeared the fourth volume of the great medical encyclopedia²⁸ begun by Follin (1823-1867) and completed after his death, by Duplay. In this treatise, Duplay repeated his recommendation to employ the eponym for the peculiar entity described by Menière, but as in 1872, he was not as precise in his specifications of the malady as he had been in his original report. Furthermore, his 1863 report of the pathological findings in the famous autopsy described by Menière had changed, and by 1875, instead of the earlier "reddish

plastic lymph of recent formation," it was now "a hemorrhagic exudate in the semicircular canals." Other signs, such as the erroneous identification of Menière as Paul, point to the suspicion that Duplay, a busy surgeon and extraordinarily prolific writer, may have found it necessary to employ assistance in his literary output. The standard work of Follin and Duplay was undoubtedly widely read and is generally but incorrectly quoted as containing the original suggestion for the eponym. A more liberal interpretation of Menière's original wording by the editors, or possibly a *lapsus calami* by an assistant could account for the inconsistency in describing the pathologic findings. This may have been the source of error that M'Kenzie was unable to discover and it may have marked the beginning of the drift toward the prevalent but erroneous belief that Menière had called the lesion in the labyrinth a "hemorrhage" or an "apoplexy."

Duplay cannot be held responsible for all the subsequent confusion concerning the pathology of Menière's disease, as he himself seems to have had considerable insight into the true meaning of Menière's report. Moreover, he was not alone in his rather free rendition of Menière's original statement. Knapp, in 1872, also published a thorough review²⁹ of the subject in an American journal and made Menière's findings familiar to English readers. In this article he said, "the pathology of Menière's disease is most probably hemorrhagic or serous inflammation within the whole labyrinthine cavity, and he suggested "apoplectiform deafness" and even "apoplexy into the labyrinth" as alternate names for the condition. Statements attributing Menière's disease to a hemorrhage into the labyrinth were a natural consequence. Without doubt, much of the difficulty arose through uncertainty in the interpretation of Menière's original words "une matière rouge, plastique, sorte d'exudation sanguine." Exaggerated concern by later writers over the exact pathologic diagnosis in a single autopsy obscured Menière's genuine contribution. The resultant perversion of the correct sense of his discovery still causes confusion in the literature to the present day.

The name, "Maladie de Menière," was immediately adopted after 1872 as a useful designation for the new entity and as a proper tribute to its discoverer. It rapidly appeared in English as "Menière's disease," in German as "Ménière-sche Krankheit," and in the latinized form as "morbus menieri" (also as "morbus meniere"). Nevertheless, the disease remained obscure, its etiology unknown, and its pathogenesis speculative; since the attacks were never fatal, material for pathologic study was unavailable. Although nothing in nature can be delimited with absolute exactness, the concept of disease entity im-

plies that any particular illness has a specific cause or, at least, a certain invariable prerequisite; accordingly, "Menière's syndrome" or "Menière's symptom complex" was substituted by some writers for the original term.

A syndrome is defined as a composite group of signs and symptoms which occur in combinations sufficiently often to be recognized as an entity; the evolution and final recognition of the component parts may require many years, and the same syndrome may arise from many different causes. Hence, the use of the term in this instance caused a loss of precision without a corresponding increase in understanding. The terminology applied to aural or labyrinthine vertigo soon became ambiguous, and by 1895 had become chaotic. Vertigo was considered to be the cardinal symptom, and the term, "Menière's syndrome," came into general use to designate attacks of vertigo when associated with tinnitus and deafness, irrespective of the cause. Some writers attempted to restrict the meaning of "Menière's syndrome" to a semblance of its original concept; others included within its scope symptoms caused by vascular disorders, infectious and toxic processes, tumors, trauma, and even hysteria. Limits for classification were never unanimously defined. It is understandable that Bárány,^{30a} and later Alexander,^{30b} advocated that the terms, "Menière's disease" and "Menière's symptom complex" be abandoned on the ground that they were equivocal and that their use impeded the further study of internal ear disease. A number of authors, however, continued to use the terms in accordance with their own definitions of them.

The confusion was compounded by the invention of the unfortunate term "Pseudo-Menière's syndrome" or "symptom complex" which Frankl-Hochwart³¹ reserved for paroxysmal attacks of vertigo and tinnitus in the presence of an apparently intact ear, unaffected by external influences. In this category, he included vertigo associated with hysteria, with the epileptoid state, and occasionally with migraine and hemicrania. Other writers borrowed this term and expanded its use to include conditions remote from anything envisioned by Menière; soon it lost all meaningful significance in the nosology of internal ear affections. In recent years, however, it is being employed with greater logic by Lindsay³² and others to designate vertigo with no auditory disturbances or central neurological signs.

In 1938, Hallpike and Cairns³³ secured specimens for microscopic study from patients who had suffered from Menière's disease, and found a dilatation of the endolymphatic fluid system. Since that time, the pathologic basis of the disorder has been explained on the

theory of hydrops, and the term, "endolymphatic hydrops" (or "labyrinthine hydrops" or "hydrolabyrinth") is generally being used synonymously with Menière's disease. With increasing comprehension of the disease and better interpretation of its diagnostic aspects, the expressions, "Menière's syndrome" and "Menière's symptom complex," should become obsolete.

A student of Menière's life and work is struck by a curious fact. Although Menière died just one hundred years ago, there is considerable confusion concerning the actual name of the discoverer of the disease, both the identity of his first name and the spelling of his surname. A physician named Paul Menière was writing in the French medical journals at the same time as Prosper. Since the latter always signed his articles in the fashion of the times as simply P. Menière, it is easily understood how his works might be attributed to Paul. This mistake happened in several influential papers published on the subject, such as that by Knapp²⁹ in English and the monograph by Frankl-Hochwart³¹ in German. Even Emile Menière, Prosper's son, is sometimes credited with his father's discovery. Wells³⁴ explains this error by the fact that Prosper Menière was a general practitioner who described the disease near the close of his career. On the other hand, the son was an otologist of distinction, who through his own writings was responsible for a measure of the recognition accorded his father.

The surname itself appears in the literature in three different ways: Menière, Ménière, and Meniere. One finds no uniformity of spelling even in the lifetime of Prosper, who in his original works always wrote his name as Menière; his son, however, at least after 1862, wrote both his own and his father's name as Ménière. In the published official transactions of the 1861 meeting of the Paris Academy of Medicine, and in the subsequent reports in the Gazette, the name appears as Ménière. Among his contemporaries, the clinicians Trousseau and Charcot and the otologist Triquet wrote it as Ménière, while the surgeon Duplay used both spellings at different times. The German otologists Politzer and Von Trötsch used no acute accent, while the American Knapp did. An interesting juxtaposition of the two earlier spellings occurred in the official record³⁵ of the eulogies given at Menière's funeral by representatives of two eminent professional bodies (M. L. Orfila—Faculty of Medicine—Menière; Barth—Faculty of Medicine, and Vaïsse—Imperial Institute for Deaf-mutes—Ménière). Both spellings are found distributed in the German literature during the following century, while in the French and English literature, the spelling is almost exclusively Ménière. Blumenbach³⁶

discovered that the change in spelling occurred in the middle of the 19th century, but that Menière himself seems to have been one of the few who continued to spell his name in the old way. Although no reason for the change seems to have been advanced, a changing pronunciation could be the explanation. In deciding the correct spelling, Menière's own choice should carry some authority even though his was not the customary spelling of the time.

As might be conjectured, the name Meniere, without accents, appears sporadically in the English literature. Shambaugh³⁷ employs this form in his recent textbook on otology. The English practice of dropping accents from borrowed foreign words is not rare, and innumerable examples among common nouns readily come to mind: elite, detour, regime, depot, cretin, clientele, confrere, rale, and others. Similarly, proper nouns include Napoleon, Orleans, Moliere, Ampere, and Barany at times. Since the term "Meniere's disease" has become popularized, it may be better to have it fully anglicized as well.

The fact that the eponym has survived years of controversy demonstrates its serviceability at a period when the nature of the disease was obscure. An eponym has the advantage that no hypothetical implication is attached to it. Now that the pathologic basis of the condition is presumably understood, there is a tendency to substitute the term "endolymphatic or labyrinthine hydrops" for the original name. It is questionable whether these rather ponderous terms will supplant such a familiar and established name as Menière's disease.

In addition to supplying an eponym for the classical disease complex, Menière's name has enriched otologic nomenclature with a number of related terms, such as Menière-like (symptoms), menieriform, Menière's triad, menierism, status meniericus, menierist and menierology. These words are found in the medical literature of the past, and some are still being used. It might be interesting to examine what contribution the name could make in the future.

First, the prefix in the term "pseudo-Menière's disease" or "syndrome," as currently understood, is not the best. The use of a word which invites loose interpretation is not desirable, even though some cases of vertigo defy strict classification. It is now recognized that the constant and diagnostic features of true Menière's disease are the auditory disturbances. Lindsay³⁹ suggested the term "pseudo-Menière's syndrome" for the atypical form which does not present cochlear signs or symptoms. He³⁸ pointed out, however, that this type of vertigo is often followed by the features of true Menière's

disease. Other writers apply the term in cases where vertigo is not yet manifested. In both instances, the attacks might be a sign of true Menière's disease if at a later period both cochlear and labyrinthine signs supervene. The qualifying prefix "pseudo," with its connotation of spuriousness, seems inappropriate for atypical cases in which it is not possible, in our present state of knowledge, to make a more definitive diagnosis. It is proposed that the term, "para-Menière's disease" (Gr. para—beside, irregular, abnormal) is etymologically more correct and that it more truly represents such cases. If this is so, the term, "ortho-Menière's disease" (Gr. ortho—straight, regular, true) could logically be applied to the typical form of the disease. At the risk of complicating the terminology, the term, "meta-Menière's disease" (Gr. meta—after, beyond, subsequent) might be used to designate the disease when it has progressed until irreversible changes have occurred in the internal ear, resulting in permanent loss of hearing.

Secondly, it is well known that recurring attacks of Menière's disease frequently produce a state of anxiety, which some neurologists speak of as a *menière neurosis*, or *menierism*. Conversely, although the condition is known to be due to involvement of the endolymphatic system, it is conjectured that autonomic dysfunction is the etiologic agent. This dysfunction may be due to cholinergic preponderance and some inherited constitutional tendency also seems to be involved. The neologism, "*menierosis*" (Gr. *osis*—condition, state, process) is suggested as applicable to this abnormal state.

Finally, there is little doubt that lack of reliable methods of physical measurement has retarded the development of otology for many years. The remarkable progress of audiology in the last three decades, since the invention of scientific audiometry, sustains this belief. The unit of loudness of sound, the decibel (an eponym itself), is an essential constituent in the computation of hearing ability. Vestibular function, however, still lacks an accurate method and a standard to register its activity. Recognition of this deficiency has led to a wide range of modern research efforts in electronystagmography and cupulometry. If, through advances in electrophysiology, it becomes possible to measure and chart vestibular function, it may then be necessary to devise a unit of activity. What word would be more fitting than the common noun, "*meniere*"? Many scientists have been honored in this way; a notable example is Ampère, a compatriot of Menière.

Whatever purpose the future may hold for it, the eponym "*Menière's disease*" has become firmly established in the medical language.

It merits continued acceptance, both for its usefulness and its commemoration of a man who had the ability and opportunity to make a fundamental scientific discovery. The man himself has been somewhat overshadowed by his famous eponym, but after a full century he is perceived to be no diminishing figure, but truly one of "the great doctors." The eponym perpetuates the name of Menière for the discovery of a specific disease and a description of it so complete that little of consequence has been added in a hundred years. The greater achievement of Menière, however, was the identification of equilibrium as a function of the internal ear. At that point, otology became a science capable of discerning the real nature and significance of vertigo. Few instances in the annals of medicine seem more deserving of the tribute expressed in the lines of Byron:

*"But these are deeds which should not pass away,
And names that must not wither."*

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XXVI

A CONSIDERATION ON THE CIRCULATION
OF THE PERILYMPH

AN EXPERIMENTAL STUDY

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The fate of the perilymph is one of the most interesting problems in otology.

Developments of the technique of micro-quantitative analysis and utilization of radio-isotopes have gradually revealed details of the components and sources of the fluid. Many investigators have agreed that continuous and dynamic flow of the perilymph exists in the labyrinth.¹ The fluid partly comes from the cerebrospinal fluid via the cochlear aqueduct. Other possible sources are the spiral ligament, especially the network of small vessels in the upper part of it, and the endolymph. Where absorption of the fluid takes place is uncertain. It is said that the spiral ligament is responsible for the absorption.

In this presentation, the site and course of perilymph absorption are discussed from the viewpoint of vascular structure of the venules in the lower spiral ligament. With the problem of the source of the fluid we are not here concerned.

METHOD

Healthy adult guinea pigs were used in the series of experiments. They were narcotized with intraperitoneal administration of 25%

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urethan (4 cc/kg). An incision was made parallel to the inferior border of the external auditory meatus. Then, after separation from the surrounding tissues, the cartilaginous external auditory canal was opened. Finally, the tympanic membrane and the lateral wall of the bulla tympanica were removed, exposing the cochlea. The round window of the cochlea was clearly under observation.

Experiments were divided into the following three groups:

1. A small amount of 1% trypan blue solution was injected into the perilymph through the round window. About two hours after injection, the bony capsule of the cochlea together with the spiral ligament and stria vascularis was taken out en masse from the basal coil to the apex. The internal surface of the fragment was examined in regard to the distribution of the dye.

2. Bromsulphalein sodium solution (5%) was used instead of trypan blue. Immediately after removal of the fragment of the cochlea, a drop of 7% sodium bicarbonate solution (per injectione) was added to it under microscopic observation. Appearance of color was observed.

3. Bromsulphalein solution was administered intravenously (200 mg/kg). After five minutes, a fragment of the cochlea received the same treatment mentioned just above. At the same time, the concentration of dye in the blood was measured.

RESULTS

1. All of the lower spiral ligament was colored blue. The attachment of the basement membrane to the spiral ligament was especially darkly colored. In the basal coil, dye was detectable also in the perivascular spaces around the venules, indicated by blue parallel lines. Faint blue color was observed in the upper spiral ligament. However, the lateral wall of the scala media was not colored. Reissner's membrane attached to the border between these zones.

2. Under microscope the freshly removed fragment of the cochlea including all coils did not show any particular change in color. However, as soon as sodium bicarbonate solution was applied, the internal surface of the fragment partly colored purple. The distribution of color was nearly the same as in the case of trypan blue injection. The attachment part of the basement membrane colored darkly. The thicker part of the spiral ligament below and behind

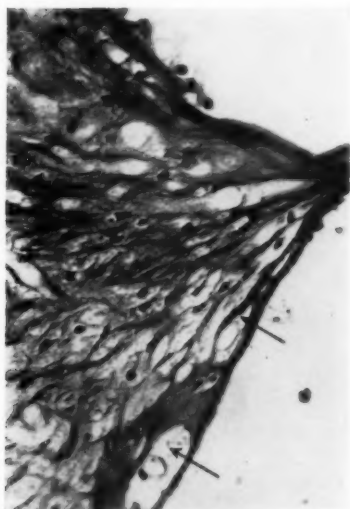


Fig. 1.—Perivascular spaces around the venule in the lateral wall of the scala tympani (the basal coil).

the stria vascularis was also stained. Purple color was observed in the venule and the perivascular space around it in the basal coil. However, within several minutes after removal of the fragment of cochlea the venules became empty, whereas in the perivascular space the colored fluid remained. In the upper spiral ligament, color was detectable along the radiating arterioles.

3. Changes observed in the lower spiral ligament were similar to those mentioned above. Bromsulphalein was demonstrated in blood obtained from the heart.

COMMENT

The function of the venule is generally considered relevant to absorption of the materials from the tissue into the blood stream, since Starling's postulate has prevailed. As to absorption of the perilymph, Mygind² was of the opinion that it took place in the spiral ligament. Arnvig³ demonstrated in the guinea pig that absorption of India ink which was injected into the subarachnoid space occurred partly through the lateral wall of the lower spiral ligament into the vessels.



Fig. 2.—Perivascular space around the v. spiralis posterior.

Using a similar method, Kley,⁴ Altmann and Waltner⁵ also found the dye in the venous vessels and perivascular space around them in the spiral ligament and vestibulum. They considered that the main site and course of absorption of the perilymph was the venous system. According to Svane-Knudsen,⁶ absorption of the cerebrospinal fluid took place at "vas scala angulare" in the spiral ligament near the basement membrane.

Direct injection of the dye into the perilymph seems to be better to obtain higher concentration of the dye instead of the method through the cochlear aqueduct. Marked coloring of trypan blue was found in the perivascular space of the basal coil and lower spiral ligament especially upper part of it, of the other coils. Dye-stuffs, however, are generally highly toxic and foreign substances to the animal. Therefore, instead of them, we used bromsulphalein solution which colored purple when it met with alkaline solution such as sodium bicarbonate solution.

Histological study of the cochlea revealed the existence of a large perivascular space around the venule of the basal coil and the v. spiralis posterior in the modiolus (Figs. 1 and 2).

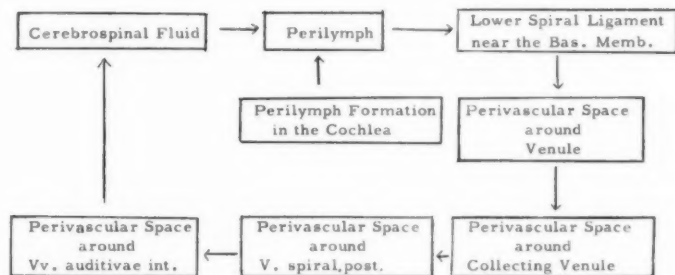


Fig. 3.—Schematic drawing of absorption and flow of perilymph.

It is possible that this space merely contains air, or perhaps it contains fluid, including perilymph, or extravascular blood plasma.

Dark purple observed in the lower spiral ligament, especially at the attachment part of the basement membrane probably indicates active absorption of bromsulphalein from the perilymph.

Color in the perivascular space around the venule is explicable in this way. Bromsulphalein was absorbed partly into perivascular tissue near the basement membrane and flowed further into the venules and the space around them (Fig. 3). These results favor the possibility that fluid exists in the space.

According to Leo Sapirstein,⁷ the volume of plasma as measured in the animal was much greater than that obtained from calculation. He believed that this indicated extravascular plasma around the capillaries.

If the perivascular space discussed here has extravascular plasma, bromsulphalein injected intravenously should appear in the space provided the concentration is sufficient. However, the matter is not simple. The wall of the venule in the lower spiral ligament is permeable to trypan blue and India ink.⁸ These facts suggest that the wall of the venule is leaky and not a semipermeable membrane. Therefore, it is difficult to ascertain whether coloring of the space is due to colored plasma or altered vascular permeability which permits escape of bromsulphalein into the space. Absorbed perilymph in the perivascular space goes back probably to the cerebrospinal fluid. Figure 4 indicates a probable route of circulation of perilymph, though it

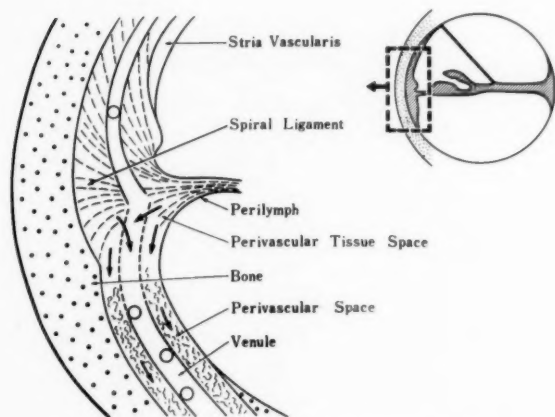


Fig. 4.—A route of circulation of the perilymph.

may occur elsewhere in the cochlea. The dye in the space remained for a long time chiefly because of the presence of a mesh-like structure in it, whereas it disappeared early in the vessels.

Therefore, flow of perilymph to outside the perilymphatic space was more rapid by way of the blood stream than that through the perivascular space. As is the case of formation of the perilymph, the absorption may take place in different places within the cochlea. Permeability of the venule wall in the lower spiral ligament, however, may play an important role in fluid transportation between the blood and perilymph for both directions.

It is not certain how bromsulphalein gets to the radiating arterioles. Three routes are conceivable:

- 1) Perivascular space around the venule - modiolus - perivascular space around the radiating arteriole.
- 2) Perivascular space around the venule - perivascular space around the radiating arteriole of the other coil just below.
- 3) Absorption of bromsulphalein into the upper spiral ligament.

SUMMARY

A route of circulation of the perilymph in the cochlea was suggested. The perilymph was absorbed in the lower spiral ligament

near the basement membrane. The perivascular space around the venule and vein plays an important role as a channel to convey fluid out of the perilymphatic space.

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XXVII

TITRATION:

EVALUATION OF AN OFFICE SYSTEM OF ALLERGY DIAGNOSIS AND TREATMENT: ITS USE IN OTOLARYNGOLOGY

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The purpose of this paper is to discuss three years' experience with a method of allergic treatment based upon titration testing to determine sensitivity known to its devotees as "titration." It was devised by Rinkel¹⁻³ after modifying Hansel's⁵ concept of "low pollen dosage." Titration, as it will henceforth be called, was inaugurated in my office practice without previous experience of any kind in allergy. To date no systemic reactions have been produced. This single statement may make the study of it worth while.

The particular geographical area in which this study was conducted was noteworthy in that it combined arid areas with a fertile valley, irrigation being the main source of water. Elm trees abound while salt cedar grows in saline areas. Mountains can be seen in the distance. The pollens of mesquite, *Atriplex* (shad scale or rabbit bush) or salt cedar may furnish an inhalant pollen all summer long. Sage abounds to the north and east and in no other directions. Some pollens, due to lack of rainfall, may never fully deteriorate but lie dormant on the ground for long periods. Dust storms, therefore, nearly always produce symptoms in sensitive individuals. A combination of such circumstances and features, coupled with the fact that many allergic people come to this type of area, results in a high incidence of allergic complaints.

This paper considers definitions, materials, diagnosis, treatment and results in connection with the method and my conduct of it.

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The literature on titration is somewhat scant.¹⁻³ Since the original publication, newer information⁴ has been obtained and numbers revised so that if more than 9 dilutions are made they will run numerically 10, 11, etc.

My original work was conducted on Bermuda grass pollen and Bermuda grass fiber sensitivity, mixtures of junipers alone and in combination, and upon the so-called minor molds. Two hundred and eighty patients, whose symptoms were severe enough to require treatment mixtures, were studied. These patients represented all such cases in the past three and one-half years.

Definitions for the purposes of this paper are as follows:

Allergen. The allergens considered in this paper are the pollens and non-pollen inhalants, i.e., dust, molds, and animal danders.

Whealing Response. The response of the skin of an individual to intradermal serial dilution testing is not satisfactorily explained by any theory of allergy. It is defined by Rinkel^{4,6} as "the occurrence, size and duration of skin reactions to the cutaneous or intracutaneous introduction of extracts of common allergenic substances as well as the factors modifying such responses" and the term is here so used.

End-Point. That point in serial dilution testing wherein the introduction of 0.01 cc of the allergen into superficial skin is followed by whealing of a certain predictable size and character at the end of ten minutes is called the end-point of reaction. The skin wheal "end-point" is usually seven mm in size. If followed by wheals (if testing successive dilutions of five times each) of nine and eleven mm size, a seven mm and nine mm combination is necessary to diagnose the "end-point." This factor makes treatment possible in testing when the dosage schedule outlined herein is considered.

Dosage. That amount of allergen in end-point dilution or its equivalent multiple, administered to secure patient relief. The schedule both as to dosage and frequency of administration varies with locality and the usual end-points found in localities according to individuals tested. Serial dilutions of this exact nature make error in treatment (and production of systemic reaction) highly improbable—if the treatment schedule is followed; care is utilized in preparation of dilutions and cross-contamination is avoided.

Cross-Contamination. The introduction, during testing or treatment, of a stronger dilution into a weaker, or an allergen of different type into a serial set of dilutions by carelessness. When this occurs the solutions must be discarded at once and new ones prepared.

Shock-Organ. That organ or system responding to the allergic insult in a highly specific manner.

Primary Pollen. The pollen capable, in itself alone, of initiating symptoms is the primary pollen of a given season.

Secondary Pollens. The pollen or pollens which may initiate symptoms in combination with other primary or secondary pollens.

MATERIALS FOR TITRATION

A. *The Table.* An orderly and systematic arrangement of solutions, syringes and dilutions is obtained by construction of the titration table shown in Figure 1. A Lakeside® No. 31 stainless steel table is the basic equipment to which other items are added. Stainless steel tubing of $\frac{1}{2}$ inch outside diameter, polished and affixed to a $\frac{3}{4}$ inch bar of extruded aluminum is utilized for syringe holders. The tubes are secured to the rod by forcing them into holes exactly $15/32$ of an inch in diameter bored into the rod. Into each of these tubes is placed a specific syringe for a specific allergen in serial dilution. At the butt of the syringe a ring of rubber tubing is found. This prevents breakage of the syringe upon return to the holder. The syringes, test dilutions and holder are labelled. The labels are then sprayed with clear Krylon®. Vials are contained and maintained in a board of hardwood or pressed wood, varnished and dust free, with sufficient holes to contain all the allergens of importance for the area. In my table the horizontal arm consists of 25 holes opposite each specific syringe with a vertical arm of 15 holes each or a total of 275 holes. These are of sufficient diameter to contain the 5 cc vials. The weaker dilutions are nearest the testing physician and the stronger solutions are nearest the syringe holder. My table was constructed from a similar photograph. Metal materials are available from steel wholesalers. Vials are obtained from chemical supply houses.

B. *The Solutions.* (All are used as syringe rinses.)

Number 1 is 2% salt, $\frac{1}{2}$ % sodium bicarbonate and 0.8% phenol in sterile water, tinted pink with aqueous saffron. It is used for extraction of dry pollen, dust and dry foods and as a preservative for treatment dilutions to be kept six weeks or longer by combining this solution with an equal amount of U.S.P. glycerine. It is known as Coca-glycerine.

Number 2 is alcohol to which gentian violet has been added. It is also used for sterilizing the skin.

Number 3 is normal saline to which 0.4% phenol has been added. It can be prepared from 0.9 grams of salt and 0.4 grams of phenol per 100 cc of water. No other solution is added to this. It, and only this solution, is used in preparation of the testing dilutions.

C. *Dilution Strengths.* These are pollen concentrates 1:20 and Endo purified house dust concentrate 1:200. (Note that they are 1:5 dilutions starting with the concentrate and that all references to house dust in this paper are to a purified Endo's house dust.)

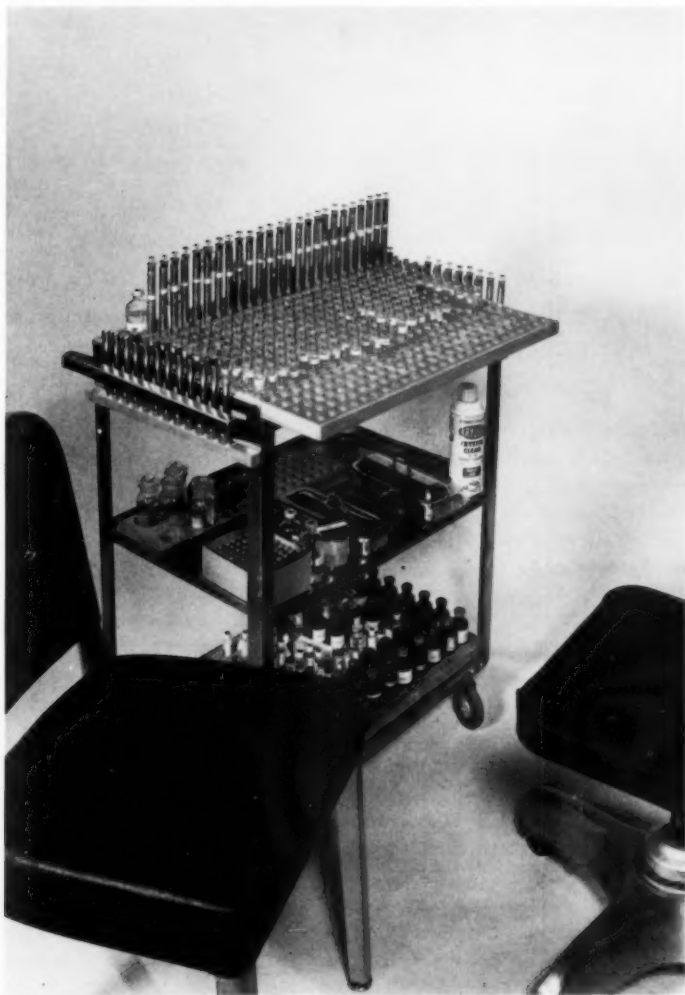


Fig. 1.—The titration table. Ledge at rear of top contains the vials and syringe holders, and holds various rinses, cotton and diluent. Second shelf shows smaller board for hospital use, vials, sterile needles and syringes and timer, *Krylon*. Bottom shelf contains concentrates. The table is on casters. The chairs show relative positions of tester and patient.

Not shown is another table with top for writing while testing three or more patients.

<i>Pollen</i>	<i>Dilution No.</i>	<i>House Dust</i>
1:100	1	1:1000
1:500	2	1:5000
1:2500	3	1:25000
1:12500	4	1:125000
1:62500	5	1:625000
1:312500	6	1:3125000
1:1.6 million (approx.)	7	1:16 million (approx.)
1:8 million (approx.)	8	1:80 million (approx.)
1:40 million (approx.)	9	1:400 million (apprx.)

In preparing these dilutions, which may be diluted further for known highly sensitive patients, the needle, hub of needle and syringe tip are assumed to hold 0.05 cc. Therefore, if 5 cc is made up for each vial, 4 cc of the Number 3 solution is placed therein. Then 0.95 cc of the allergen (plus the 0.05 cc unmeasured) concentrate is rinsed into the first vial. A similar amount is then taken from the first to the second vial and through each subsequent dilution.

D. The Rinse Technique. Two syringes are rinsed at a time. The testing dilution remaining in the syringes is ejected into the waste bottle on the ledge in back of the syringe holder. They are then rinsed three times in No. 1 solution, the waste being caught in the waste bottle. Then they are rinsed three times in the No. 2 solution, ejecting the first rinse into the waste bottle. Then the two syringes are rinsed three times with No. 3 solution. Each syringe must be filled to the 0.6 cc mark in each rinsing.

Each needle is autoclaved after use. The syringes are rinsed following removal of the needle. Rinkel⁷ has overcome this difficulty by devising a rapid needle changer and rinsers with autoclave between usage.

E. Syringes and Needles. Any good standard tuberculin syringe may be used provided it is graduated in 0.01 cc and 0.05 cc. Vim[®] needles are preferred because they seemingly do not break but tend to hold together rather than to snap completely off. Some prefer the B-D[®] needle because the bevel is on the same side as the trademark which may make for speedier titration. The needles are one-half inch

Antigen	12	11	10	9	8	7	6	5	4	3	2	1	Amt. No. Set
Ragweed-M.													
Ragweed Repeated													
Sages													
Iva Ciliata													
Pigweeds													
Pigweeds Repeated													
Kochia													
Chenopods													
Thistle													
Atriplex Botrys													
Grass													
Grass Repeated													
Plantain													
Sorrel													
Trees													
Elm													
Cottonwood													
Dust													
Dust Repeated													
Alternaria													
Hormodendrum													
Cephalosporium													
Fungi													
Smut													
Silk													

Primary set is _____ Start at 0. _____ Total of Set _____ Multiply By _____
 of the No. _____ of the No. _____ & stop at 0. _____
 Secondary set is _____ Start at 0. _____ of the No. _____ & stop at 0. _____
 of the No. _____

Fig. 2.—The card for recording results of titration.

in length and 25-gauge. Syringes are discarded at any time an air leak at barrel and plunger (caused by chipping with use) is apparent.

F. Concentrates. Endo's House Dust is distributed in 1:40 dilution and a sufficient quantity of 1:200 dilution is made up for one year's supply. Coca-glycerine is used for this purpose. In an ordinary otolaryngologic practice 50 cc will be sufficient. Concentrates of pigweed (*Amaranthaceae*), *Kochia*, sages (*Artemisia*), *Iva ciliata*, *Iva xanthifolia*, thistle (*S. pestifer*), ragweed (*Ambrosiaceae*), *Chenopodium album*, Bermuda grass, trees (mixture of minor trees), elm, cottonwood, *Alternaria*, *Hormodendrum*, *Cephalosporium*, smut mixture (grass and grain), silk (moth), histamine, T.O.E. (*Trichophyton*, *Oidomycetes* and *Epidermophyton*), and penicillin-G are always available in proper season and freshly prepared dilutions. These are freshly prepared each two weeks to insure proper potency. One serial dilution, and occasionally two, is prepared daily to lessen the task of making fourteen or more at a time.

G. Miscellaneous. Miscellaneous items as brushes (to clean the table), bottles, vials and titration forms (in different colors for the various seasons) are available. The titration card used is the same size as the record card as shown in Figure 2. A whetstone, nasal speculum (for applying stoppers to vials) and forceps are available. Stoppers are changed whenever punctured to excess.

The entire contents of the table and vials are changed completely twice yearly, and fresh labels are applied.

Successful titration depends upon cleanliness of equipment, care in preparation and use of the materials and concern for the patient.

DIAGNOSIS

The history is of primary importance in the diagnosis of allergy as in all of medicine. One must determine through skillful use of it whether the presenting symptoms are allergic in nature; whether they incriminate the offending allergen and thus eliminate much unnecessary and time-consuming testing. Extensive testing is to be considered only when one has not established or cannot establish a disease entity or identify a pathologic factor producing the given symptoms.

Eosinophilia and the pollen count are useful but not always correct in diagnosis.

First an attempt is made in questioning to determine the presence or absence of the basic symptomatology of itching of the ears, nose, throat or eyes, nasal discharge, sneezing, tickling, etc. It has been a rare occurrence, in my experience, to find a patient expressing a pure nose and throat symptomatology of allergy without other evidence in the past history of respiratory or gastro-intestinal symptoms of allergy as well.

Often an associated factor of concomitant food allergy is present although the natural immune mechanism of the patient may help overcome one inhalant allergen if not complicated by an associated food allergen. Conversely, the patient may handle his food problems without difficulty when his inhalant allergen problem is overcome by titration and treatment.

The usual symptoms pointing to the various offending factors are as follows:

A. House Dust. The house dust sensitive patient is worse inside at a time of the year when the furnaces or air conditioning are on and the house is closed. There is not much itching of the eyes but more nasal blockage, which occurs soon after the patient goes to bed. Bedding, bedclothes, and a cotton-filled mattress are the finest generators of house dust. Itching of the ears may frequently be a symptom of house dust sensitivity.

The patient may believe, because no eosinophils are found in his nasal smear, that he has no allergies and will refuse to consider allergy therapy. And yet, the patient with frequent colds, sinusitis or head trouble in winter is ordinarily a house-dust sensitive individual.

B. Pollen. The pollen sensitive patient is worse outside the house and itching of the eyeball is a prominent symptom. The patient usually gets better inside the house with the windows closed. Symptoms are often reduced with rain and increased on windy days.

C. Molds. The mold-sensitive patient is usually worse on damp or windy days and the eyelids may itch. The determining points are increase in sensitivity or symptoms "when the sun goes down," "in low places," "in the cool of the evening," or in certain areas of the home as a basement. These questions were used with perfect confidence in determining whether any patient should be tested for the minor molds, for example.

D. *Thermal Factors.* These are most important in winter and are typified by a continual and clear nasal discharge. Many seasonal hay fever patients have thermal factors which may be mitigated somewhat by small doses of histamine. These same factors may occur in an extremely cold-sensitive patient in the summertime with sudden drops in temperature.

E. *Food.* This category is inserted as a differential aid only. The important symptomatology here is manifested by its periodicity, post-prandial flares and nocturnal attacks. The patient is awakened in the middle of the night, often has insomnia and is fatigued upon arising. Frequently he has symptoms when he first arises and with a minimum of muscular effort. He represents, in these symptoms, "the sum total of yesterday's allergic insults."⁴

Missal's⁸ paper on foods as related to otolaryngology is worthy of study. No food study is accurate unless the pollen and non-pollen factors are controlled or eliminated also. Correct treatment of the pollen will mitigate the food reaction but never eliminate it entirely.⁷

Before coming to treatment, each patient is asked to evaluate the severity of his symptoms, *i.e.*, whether severe enough to merit undertaking complete allergic study and treatment; or if he desires short-range management with customary measures as anti-histamines, pre-epinephrine precursors and other medications. Ordinarily most individuals desire to try the simpler things first. If these fail to give the necessary relief, many patients desire to get to the bottom of the problem.

TREATMENT

I have never utilized steroids in treatment simply because replacement therapy can ultimately result in only one thing—disuse atrophy. Stimulating hormones such as ACTH naturally have their place in emergency conditions or in the acute manifestations of allergic disease but cannot replace logical, long-term, specific therapy.

The treatment of allergy by titration is accomplished when one first understands the nature of the whealing response of the skin as outlined by Rinkel and when his procedures, treatment schedules and other practices, determined by long experience, are faithfully carried out. The method is precise and adherence to the rules is necessary for success.

The whealing response, as defined previously, is determined by the intradermal introduction of serial dilutions, beginning with the weaker and progressing toward the stronger dilutions until there is a wheal two millimeters larger than the control or non-reactor as the case may be. Exactly 0.01 cc of solution, introduced into the superficial skin, produces a testing wheal of 4 mm in diameter. In some cases all tests applied will produce a 7 mm wheal but, in the majority, the non-reactor will be a 5 mm wheal at the end of ten minutes. If this concept is carefully followed, a frequent source of interpretative error is removed.

Successful treatment of an elm-sensitive patient with dilution No. 13 (1:25 billion) has been noted by me. Similar experience was gained with an extremely grass-sensitive patient treating with Bermuda grass dilution No. 12 (1:5 billion). Several weed-sensitive patients in the vicinity of dilution No. 8 have been discovered. Consequently "scout" tests with 1:100 dilutions of the various allergens are not run in this office for fear of producing constitutional reactions.

In co-seasonal testing and treatment, which are closely related by virtue of dilution and dosage schedules, one relies on a plant survey rather than pollen counts. This is simply a periodic study of the local situation with regard to the plants or trees of the season. A local agronomist is invaluable in the early experience of plant identification. The following pollination schedule, with variations for unseasonal temperatures, moisture and plant growth factors, is believed reasonably accurate for this area:

January—House dust, molds, and thermal factors.

February—Foregoing factors plus elms, which may be introduced late in the previous month.

March-April—This is the tree season. American and Chinese elms are found in this area. Spring "colds" are usually caused by tree pollens.

May—*Atriplex* (shad scale or rabbit bush) is a factor in this month. Grasses, plus mesquite, salt cedar, "mountain cedar" (*Juniper sabanoides*) and other juniper trees are pollinating.

June—Mesquite peaks out. Sorrels have not been a prominent cause for hay fever in this area in my experience.

The weeds may begin depending on moisture. The earliest weed in this area is pigweed. One proven case of greasewood sensitivity is known in this area and this is a profuse bloomer nearby.

July-August-September—Pigweed, *Kochia*, thistle, chenopods, and *Iva ciliata* are introduced into the allergic picture. Ragweeds and sages are introduced late in August and September. Bermuda and Johnson grass smuts locally. Bermuda grass continually pollinates and is the grass used in testing and treatment the entire period. A fall *Chenopodium album* crop is sometimes a cause of hay fever. *Alternaria* is a prominent cause of trouble in all who experience symptoms with mowing of lawns.

October-November-December—Weeds are gone with the first frost; not only of a morning frost but of a temperature of at least 25 degrees plus rain. The latter is needed to destroy the pollens already present in the dust which is in the air, otherwise, with the first windstorm. *Alternaria* may become less important than *Hormodendrum* as the period progresses. Dust, molds and thermal factors are of increasing importance.

It is always desirable to recognize the single factors causing symptoms. Treatment is best when as uncomplicated as possible. Testing and treatment are inseparable when using this method because treatment with the amount of allergen used in testing is computed in determining the first dose. In other words, the first therapeutic dose includes the amount of antigen used in determining the end-point. Only the end-point dilutions are considered as the previous 5 mm reactions are of no consequence in such computation.

The weed survey or plant survey is extended to the areas from which patients come for treatment. Therefore one must travel widely if patients are successfully treated.

Interesting responses to the introduction of material in the skin are noted. The zone of erythema around the wheal is a matter of interest only. One determines the "clear-cut end-point"⁴ by measurement of the wheal. This response of a series of 5 mm wheals followed by 7 mm and then 9 mm wheals occurs, according to Rinkel,⁶ in 72% of the cases. In the clear-cut end-point response, the first test to show erythema will most commonly, but not always, be a 7 mm wheal.

When this is followed by a 9 mm wheal the dilution causing the 7 mm wheal is taken as the end-point and is always utilized as the treatment base. It is always related to the treatment or beginning dose. Such testing must be added to the computation in figuring the first treatment dose, as is proven by patient response with such testing and therapy. In a limited number of instances, the end-point whealing response will be an eight or nine mm wheal, followed in turn by an eleven mm or thirteen mm wheal. If the preceding test were absolutely negative at the end of twenty minutes, this larger wheal is considered the end-point.

There is a type of reaction known as the plateau-type of response wherein dilutions of different strengths cause the same sized wheals (suggesting concomitant sensitizations) which must be pursued to a wheal two millimeters larger than the one preceding for determination of the end-point.

Knowing it is not possible to make a true evaluation of the end-point of reaction if the first test applied causes a definite response, we then proceed to co-seasonal testing. This is simply serial dilution testing, applying the pollens and factors presumed to be important at the time of testing and in weak enough dilution to avoid an initial response to the dilution utilized. One acquires, with two or three seasons of experience, the commonly found, average patient, end-points for the area. These may vary with moisture and other climatic factors. The allergen groups are tested applying about five or six groups at a time. Progressive testing of one or two dilutions at a time is utilized until a seven mm wheal is followed by a nine mm wheal. These are recorded with each test dilution. And it is here that the beauty and simplicity of titration is found, for it is almost impossible to discover one 5 mm whealing response, to skip a dilution and apply the next dilution with danger of overdosage. The end-point dilution and a subsequent 9 mm test results only in a 6X or a "multiple"⁴ of six as a treatment dose. The end-point, produced by 0.01 cc, is considered a 1X dose or a multiple of one. The next dilution is five times as strong or a multiple of 5 or the equivalent of 0.05 cc of the end-point dilution. One simply adds 0.01 and 0.05 to get 0.06 or a multiple of six which is expressed as 6X.

Initial doses of dust are of 5X strength; molds of 10X and pollens of 15X unless end-point dilutions are Number 1, in which case pollen and molds are reduced by 5X each. Scheduled increases of the primary pollens, dust and molds are as follows:

Dust—5X, 7X, 10X, 12X, 15X, 20X and 25X

Pollens—15X, 25X, 35X, 50X, 75X, 100X and 150X

Molds—10X, 15X, 25X, 30X, 35X, 50X except in minor-mold combinations which are 1X, 2X, 5X, 7X and 10X

Greater multiples than 50 have rarely afforded relief in this area using this method of testing and treatment. The higher (stronger) the patient's end-point the smaller the multiple as top dose and, usually, the shorter his duration of relief.

Patient relief is the criterion for treatment dosage increase. If the period of relief is satisfactory the dose is not increased. The primary pollen alone is utilized for treatment the first dose since we know that end-points may change rapidly. The patient is therefore re-checked on subsequent days until the end-points have stabilized. All dosage is computed on the basis of the original testing until this stabilization occurs. If the patient lives out-of-town the schedule is followed by giving him individual dosage bottles before having him return for re-check. When this plan has been varied for reasons of economy to the patient, the mixture is given the patient with the understanding that a subsequent re-check may be necessary. A treatment schedule is outlined using the mold schedule including dust in a multiple of one or 1X per 0.01 cc of the solution.

Testing with dust is discontinued if two successive 7 mm wheals are produced. The first 7 mm wheal is considered the end-point for treatment, just as if the second 7 mm wheal were a 9 mm wheal. In the secondary pollens we may discontinue testing with a 7 mm wheal surrounded by 25 mm erythemas.

A rapid, somewhat dramatic change in the size of the end-point wheal may be considered as "flashing" or "flash reaction."⁶ Tests are discontinued and repeated from the suspected end-point (knowing the progression of whealing under normal circumstances) until end-points progress in the customary fashion, i.e., 7 mm and 9 mm wheals for an end-point. In the event initial testing produces a 13 mm flash one may simply go back three weaker dilutions and apply a test, repeating the advance to the true or clear-cut end-point. Flash response must be eliminated in testing and one should always remember that it is not possible to make a true evaluation of the end-point of response when the first test applied results in a definite whealing re-

sponse. Rinkel's dictum of "err on the side of weaker dilutions"⁴ is a good one for all to follow, including those with experience. We have always made this a primary rule for all connected with treatment.

A patient must be treated with single mixtures of his primary pollen or with single factors at first. This reduces the number of allergens within the mixture to be used in treatment and enables one to evaluate the patient's response to treatment. The patient returns as soon as relief has worn off if more than 24 hours elapse. If no relief is obtained, he empirically returns within 96 hours. One should have relief and improvement within the hour following injection if successfully following this method of treatment. A most dramatic response to treatment in children, in my experience, has been the profound improvement in temperament and disposition.

PREPARATION OF THE TREATMENT MIXTURE

Rebhun⁹ originally thought that certain plant fibers would act as allergens if crushed fine enough for inhalation. Because Bermuda grass dries so completely in winter in this area and is reduced to dust, I have introduced bermuda pollen into our winter allergenic mixtures with apparently good results. Since the present study does not seem to substantiate this practice, it will be eliminated and re-introduced in winter studies this year.

First, the patient is given a page in a notebook and a number for his mixture, which number is always constant. The important co-seasonal factors are listed under his name for this and all future reference as to dosage. In mixtures one may reduce the maximum pollen dosage to a multiple of 50 (50X) and, when dust is added, a maximum of 25X for this allergen. It is known that patients may often fail to tolerate dust or molds in the same treatment mixture with pollens due to the factor of "antigen incompatibility."⁴ Yet one must attempt to make all mixtures combine the important co-seasonal factors where possible for simplicity of administration by the patient. It seems that the first year of treatment is usually the one of best results. A patient frequently accepts a breakdown of treatment mixtures more readily after an initial period of satisfactory treatment by one injection given weekly or less often.

My out-of-town patients are encouraged to give their own injections. A detailed printed schedule is given each. This practice seems to give the patient an increased consciousness of his problem.

In compounding the treatment mixtures the ultimate maximum dosage of 50X pollen, 25X dust and 50X mold are considered. With this concept, each 0.01 cc of the mixture must contain 2X pollen, 1X dust and 2X mold. The allergens to be placed in the mixture are listed. One then proceeds two dilutions beyond the end-point (25 times as strong) and draws up 0.02 cc or 0.01 cc with the labelled syringe for each separate antigen. The required number of doses for each is considered. In other words, the end-point is the equivalent of 1X, the next stronger dilution is equivalent to 5X and the next stronger dilution is equivalent to a multiple of 25 or 25X. If 0.02 cc of the dilutions 25 times as strong as the end-point are utilized, a multiple of 50X is obtained for each. If 0.01 cc of this dilution is utilized for house dust, a multiple of 25X is obtained.

Each of my local mixtures for the patients studied contains seven full 50X doses of pollen and seven full 25X doses of house dust. This number of doses corresponds more closely, in my experience, to the growth periods of plants and duration of the various growing seasons. Therefore 0.14 cc of each pollen antigen or 0.07 cc of the proper dust dilution is withdrawn and injected into the mixture vial without pumping the syringe plunger. In the event minor mold mixtures are utilized as well, a multiple of 25 is utilized for them as with house dust. These figures are totalled for the number of allergens in the mixture and subtracted from 1.75 cc (seven full doses of 0.25 cc each). The required amount of Coca-glycerine to bring the total amount to 1.75 cc is added as diluent because the mixture ordinarily will be utilized for more than six weeks of treatment.

The three most important considerations of the therapeutic program are: interval of the dose, rate of dosage advancement and determination of maximum optimum dosage. My custom is to follow Rinkel's rules^{4,6} in this regard. The interval between doses in days (24 hours) is indicated by the number of the dose, *i.e.*, two days for the second, three days from the second for the third, *etc.* One must continually strive for a maximum period of relief and when this is not obtained he can either re-check or go back to the dose giving the maximum period of relief, repeating this amount at the pre-determined interval. Ordinarily patients who have optimum relief have no visible redness or swelling at the site of injection four hours after treatment. The patient must orient the physician as to the maximum optimum dosage. This amount is then utilized for successive treatments considering the greatest time interval and most relief possible. The treatment schedule for the two hundred and eighty patients studied has been that of the schedule for molds with the mixture

containing a maximum multiple of 25 for dust in almost every instance.

An occasional patient may require a larger amount of house dust and this, too, may be increased to a 50X dose maximum although re-check may demonstrate a change in end-point. When this occurs a new mixture with maximum dose of 25X for dust is usually satisfactory. For those who cannot tolerate the dust, mold and pollen mixtures together, separate vials are given the patient for administration on separate days. This is considered due to antigen incompatibility.

Treatment failure is ordinarily due to this factor of antigen incompatibility. In my experience this is frequently manifested by unusual itching of the skin. Other factors modifying the ultimate treatment response are: treatment itself, concomitant foods, tree pollens, over-dosage and excessive initial dose.

Co-seasonal treatment failure is best analyzed by study of the patient's symptoms, as Rinkel⁶ advises. If the patient is worse, despite treatment, from 8:00 AM to 11:00 AM, better in the afternoons, worse in the open and better indoors, worse with high winds and has bulbar conjunctivitis, one must think of pollens or rare pollen inhalants which have been overlooked. One may eliminate *Chenopodium album* early in the summer season, as an example, forgetting that there is a fall chenopod season with certain climatic factors.

If the patient has no conjunctivitis but itching of the eyelids, yet has a severely blocked nose, is better in the open than in the house, has trouble as soon as he lies down in bed, is worse in cool air, or has abrupt increases within 15-30 minutes of certain meals, one must suspect dust, mold and food allergies as being out of control. Utilization of re-checks, at no charge to the patient, is the best means, in my hands, of overcoming treatment failures. These will occur when patients are at some distance and local factors are unknown for the area in which the patient resides.

In conclusion, there are individuals who are unable to gain long periods of relief and must, of consequence, take a smaller dose at more frequent intervals. This is true if a larger dose makes them worse or gives no relief. Many times these patients represent complicated sensitizations plus endocrinologic, psychogenic, food and other factors. This has been particularly true in coincident cases of asthma which are successfully controlled with relief of nasal symptomatology and then,

quite suddenly, go out of control. These patients may require the time-tested remedies of adrenalin, ephedrine and calcium. It behooves the otolaryngologist to let cases complicated by asthma alone until experience is gained and then never to treat them without the benefit of good internal medicine consultation and collaboration.

RESULTS

Of 280 patients, for whom mixtures have been made initially over a period of three and one-half years, the results are shown according to presenting complaint and results of management in Table I. It should be borne in mind that this number is not large but the titration and antigen mixing are done by the physician. In every instance these were individuals who had tried the usual methods including antihistamines but finally desired efforts at hyposensitization.

In this series the results are divided into fair, good, excellent and failure. Fair results include those individuals who failed to return after a short trial for re-checks since they did not understand the problem of changing end-points. They also included the first patients seen under very unsatisfactory testing conditions. The good patient results are those with relief of some but not all symptoms. Excellent results are denoted for those in whom all the presenting complaints were relieved. Failure is used when the patient's history was reviewed and repeated attempts at control were unsuccessful or any of a variety of reasons. These failures accounted for six per cent of the total.

Peculiarly, many of those individuals in the category of fair results for whom only one or two mixtures is made will, when seen a year or so later, state they have had no more trouble. Then they will re-appear at a similar season as when first seen. Fair results comprise 14.3% of the total.

In reviewing the individual failure cases I noted that there were several causes which were not the usual reasons listed by authoritative work on the subject. Some of these were attributed to enthusiasm; others to faulty history taking and interpretation of symptoms; previous steroid treatment (which may result in a very bizarre whealing response); expecting too much from a good method applied to an unsatisfactorily selected or poor case. A poor case would be represented by one from whom other allergists have experienced similar difficulties for several years. Failures may occur in overlooking border-line surgical indications, and in two of our ear cases failure was attributed to difficulty in patients returning to this office from another

TABLE I
SUMMARY
OF
280 CASES

PRESENTING CONDITIONS		AGE	TREATMENT DISCONTINUED	PRESENT TREATMENT	CONTENTS OF INCOMPATIBILITY MATURE	ARTIFEN INCOMPATIBILITY	EVALUATION OF INCOMPATIBILITY COMPONENTS	RESULTS OF TREATMENT IN TEST	OTHER METHODS UTILIZED	INHERENT FAILURE					
1	2	3	4	5	6	7	8	9	10	11					
1-SECONDARY SYMPTOM COMPLAINT IN ADDITION TO OTHER FIGURES IN BOXES	PRESENTING CONDITIONS	INFANTILE	9	3	2	1	2	7	6	3	1	7	1	1	
		ADULTS	12	10	12	4	1	5	17	19	3	8	13	1	1
		WITH ERYTHRO	2-5	12	4	1	5	17	19	3	8	13	1	1	
		CHILDREN OTHER	6	10-15	5	4	2	10	21	17	4	2	14	1	2
		ITCHING	3-5												
		POST-OPERATIVE ERYTHEMA	3-5												
		ITCHING	3-5												
		ITCHING	3-5												
		ITCHING	3-5												
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city. No similar facilities were available to them for the re-checks made necessary by changing end-points.

In considering the table it is believed that the greatest number profited from anti-allergic management and that all would not have done so well without this management.

SUB-MIXTURE STUDIES

1. *Bermuda Grass Pollen and Bermuda Grass Fiber.* Attempts were made in a series of twenty-five of the above cases during the current year to demonstrate like sensitivity of the patient to Bermuda grass fiber and Bermuda grass pollen dilutions. There was no constant similarity, in any individual, of fiber end-point and pollen end-point. Relief was not obtained in any known sensitive patient by substitution of fiber for pollen antigen. In cases where fiber was used in testing the patient did not secure relief from symptoms. Most of them wanted to discontinue because none was desperate enough to continue in the face of failure. On the other hand these same patients seemed to experience prompt relief with administration of the proper dose and dilution of grass pollen. This dose, locally, has varied from a multiple of 25 to one of 60 for the past two years.

In my experience the most sensitive patients to Bermuda grass pollen have been children who presented associated itching legs (before *Kochia* is pollinating) from walking in the grass. They ordinarily have had a treatment end-point at dilution Number 6. These same patients may be, and usually are, quite sensitive to *Alternaria*. Fiber end-points, most commonly, were noted at dilution Number 1 or Number 2, the majority being at the stronger dilution.

2. *Cedar-Juniper Mixtures and Separate Mixtures.* In a botanical sense, all the cedars in this area belong to the juniper family excepting "salt cedar" which belongs to the genus *Tamarix* and is considered separately. However, there is one juniper known as "mountain cedar" which forms the basis for the differential noted above. In the testing the following concentrates have been utilized to make serial dilutions:

- a. Juniper mixture from equal parts of *J. pinchotti*, *J. virginium* and *J. monospermium*.
- b. "Mountain cedar" or *J. sabanoides*.

- c. Cedar-Juniper is made of equal amounts of the concentrates.

In my experience there is sufficient agreement in end-point to titrate with one mixture instead of two. There are large areas within this state covered with various types of juniper. The trees appear to be definite factors in my patients. One juniper was believed by some patients to pollinate the year-round. Upon survey of the area, it was my feeling that this represented pollen which had not been removed from the trees by blowing winds. None of my patients has failed to get relief on the mixture as compared to the individual trees.

3. *Minor Molds.* Two mixtures have been utilized in testing and treatment as devised by Rinkel:

- a. *Mold Mix:* This consists of equal parts of *Cbaetomium*, *Eppicoccium*, *Fusarium*, *Helmintosporium*, *Monilia sitophila*, *Mucor*, *Penicillium*, *Pboma*, *Pullaria*, *Rhizopus*, *Rhodotorula* and *Saccharomyces*.
- b. *Mold Mix B:* This consists of equal parts of *Achorion Schoenleini*, *Cephalothecium*, *Cladosporium*, *Curvularia*, *Gliocladium*, *Mycogone nigra*, *Neurospora crassa*, *Nigrospora*, *Pacc*, *spicara*, *Scopulariopsis*, *Spondylocladium*, *Stemphylium* and *Streptomyces*.

In an original report¹⁰ 25 patients in succession were tested with the Number two dilutions of Mold Mix A and Mold Mix B. Four patients were positive to Mold Mix A only and 1 patient was positive to Mold Mix B only while 16 patients responded to both mixtures. Four patients were apparently not sensitive to either dilution.

Twenty-five patients who reacted to Number 2 dilution of Mold Mix A or Mold Mix B, or both, were placed on treatment. Twenty-one were successfully treated and controlled better than before mold titration. Two old patients gave up therapy and two were considered to receive doubtful value from such therapy due to unco-operativeness or unwillingness to investigate foods.

Twenty-five patients who reacted to Mold Mix A and Mold Mix B were asked this question: "Are your symptoms worse between 5:30 PM and 8:30 PM? Are these symptoms worse in low places? Are they worse or increased from mid-July to November?"

Fifteen patients answered yes to the above question. Ten patients answered no to the question or part thereof. It was interesting that

two patients who failed to react to either mixture gave a positive answer to part or the whole question.

These results have formed the basis for application to an additional 49 patient mixtures or revisions of previous mixtures without similar statistical breakdown.

In my original study patients with the largest reaction wheal for the dilution tested lived elsewhere in the early or formative years, namely, Omaha, St. Louis, and Venezuela. Unreported was the fact that two children asthmatics with 11 mm whealing response to the Number 2 dilution were successfully controlled by the addition of the two mixtures to their regular treatment mixtures. One narrow zone of relief was lengthened in period of relief with apparent mold stabilization. Seven patients were definitely "cold" sensitive, i.e., to temperature changes at any time. Two patients were allergic to penicillin or yeast-containing foods and responded to diet. Four patients (one boy, two girls and an older woman) complained of skin eruptions in addition to other symptoms which improved or cleared with treatment. In the older woman the recurrence of the skin lesion, located on the ala of the nose, was the earliest sign of need for recheck. One child had missed 55 days of school in the quarter, and another 19, before titration. Both have been to school continuously since beginning treatment.

Since the preliminary report, these mixtures have been utilized in my local titration rather than a previous mold mixture which combined *Penicillium*, *Mucor*, *Aspergillus*, *Phoma* and *Rhizopus*. Dilutions are made in exactly the same fashion as when other concentrates are used and titration carried out as with any other mixture. The previously listed questions are asked the patient to determine his need for testing. When an individual is found with an end-point of reaction beyond Number 2 (weaker), the mixtures are incorporated in a multiple of 25X for total dose with apparently beneficial results. This is the same manner in which dust is utilized or added to the patient treatment mixtures. The most enthusiastic patients for the newer mold mixtures have come to this area from the older centers of population and other climates.

The type of cases in which the minor mold mixtures were used is shown in the table.

4. *Penicillin and Mold Desensitization in Treatment of Skin Lesions.* This dramatic means of treating certain aural conditions such as external otitis with clearing of associated lesions elsewhere on the

patient's body is mentioned to encourage further study and reporting. It is used most dramatically in postoperative aural discharge and undoubtedly is of greater value elsewhere than in this dry climate. It has cleared a profuse aural discharge in one of my patients which was cultured to demonstrate *staphylococcus aureus*. This particular individual took penicillin for each respiratory infection, was fond of cheeses and hot sauces and yet only 1.00 cc of a Number 6 dilution of penicillin-G (1:325000) in the manner described by Rinkel¹¹ completely cleared the aural discharge.

The reader is referred to the works of Brown¹² and Withers¹³ for treatment of skin lesions and other uses for T.O.E. (*Trichophyton*, *Oidomycetes* and *Epidermophyton*) antigen in otolaryngology practice.

I became interested in this aspect of certain difficult cases upon hearing one patient state he believed all his urticarial wheals of lips, eyes and temporal areas followed administration of penicillin for his chronic otitis media. I have subsequently titrated and treated any individual with either penicillin or T.O.E. in combination when he reveals his sensitivity to penicillin, is fond of cheeses or seasoning with a vinegar base. He is desensitized in the manner described by Rinkel¹¹ who has discussed these methods elsewhere.^{4,6}

SUMMARY AND CONCLUSIONS

A safe method of anti-allergic treatment, based upon titration testing to determine sensitivity, is described. This method has been described by Rinkel^{1,3} and in a series of post-graduate lectures at the University of Texas School of Medicine as well as the lecture series of the American Academy of Ophthalmology and Otolaryngology.

Two hundred and eighty cases are considered. As a result of this study the conclusion is drawn that almost eighty per cent (79.7%) of these patients obtained relief from symptoms which might not have been obtained by other methods. No systemic reactions to the method have been observed by me in the three and one-half years in which it has been used.

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ACKNOWLEDGEMENTS—My thanks go to Dr. Dor W. Brown and Dr. Ben T. Withers for their conferences on mutual problems and for their experiences so unselfishly shared.

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XXVIII

CONTINUOUS SINUS THERAPY

JOSEPH B. BIEDERMAN, M.D.

CINCINNATI, O.

Because of the anatomical position of the accessory nasal sinuses, and their narrow openings into the nasal passages, infection with resulting edema and thick secretions readily causes obstruction of the sinus openings.

The sinuses, unable to get proper aeration and drainage, become ideal breeding grounds for growth of infecting organisms. The inflamed sinuses, in addition to causing local symptoms, may also lead to complications or act as foci of infection if not properly treated.

To establish adequate drainage and aeration is the prime objective of sinus treatment. Proetz¹ states: "Ordinary nasal douches and sprays are impractical so far as intrasinus treatment is concerned, because the amount of solution which succeeds in penetrating even normal ostia is negligible. Particularly in those disease conditions accompanied by swelling, in which intrasinus treatment is expressly indicated, no penetration occurs."

POSITIVE AND NEGATIVE SUCTION THERAPY

A great advance in the treatment of sinus infections came with the introduction of the Proetz method. This method provides intermittent negative pressures to the nasal cavities, thus removing mucus plugs blocking the sinus openings and allowing for proper drainage, aeration and introduction of medication. This method of treatment has proven very effective, as verified by numerous investigators, some of whom wrote as follows:

Boies²: "Proetz Displacement irrigation . . . is especially applicable to the ethmoidal and sphenoidal sinuses. There it is effective in ridding the numerous cells of their contained mucoid or mucopurulent secretion and so restoring to normal activity, the cilia and mucous blanket."

A. H. Andrews, et al.³: "Low pressure might benefit sinus disease by any one or all of the following three mechanisms:

- 1) Provide effective suction,
- 2) Cause a vasoconstriction which would enlarge the ostia of the sinuses as well as the nasal passages, and
- 3) Increase aeration of the sinuses, due to changes in the density of the air. Such 'suction' would be devoid of the mechanically irritating effects incident to the method of irrigation."

W. W. Morrison⁴: "These solutions can be made to enter the sinus cavities by applying intermittent suction of only 3 or 4 inches of vacuum to the nose. This draws air bubbles from the sinus cavities and allows the solution to enter the sinuses."

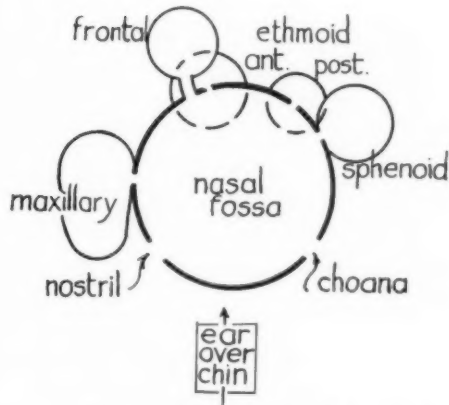
Barach, et al.⁵: "Sinus x-rays eight days after starting penicillin nasal suction treatment revealed considerable clearing of the clouding previously noted in the right antrum, right ethmoids and complete clearing of the sphenoids."

Nasal suction therapy with antibiotics and other medicaments has special merit in the treatment of sinus infections, because it enables high concentration of the therapeutic agents to make direct contact with the infecting organisms.

MECHANISM OF ACTION

Producing suction in the nose causes a vacuum to develop which, in turn, permits the air to leave the sinuses and the liquid to enter in its place. The addition of the proper therapeutic agents to the local measures to permit sinus aeration and drainage has shortened the duration and lessened the virulence of infecting agents.

About 12 hours after treatment, however, the sinus openings often again become closed and adequate aeration and drainage are again prevented. It is practically impossible to have the patient come to the office every 12 hours to take these treatments, so a means was sought to enable the patient to continue the positive and negative suction treatment technique at home between office visits. In this way, continuous sinus medication, drainage, and aeration can be maintained. The method must be simple and one that would not entail expensive equipment, must not be able to cause damage by generating too much pressure or suction, and should be able to be used anywhere.



Diagrammatic representation of the nose and its accessory chambers and openings, to illustrate their mechanical relations.

Figure 1 (from Proetz¹) shows the location of the paranasal sinuses and their openings.

In order to obtain suction in the nasal cavity, it is necessary to completely seal the nostrils while applying positive and negative pressures. The tips now used for dispensing nasal drops or sprays do not seal the external nares. It was therefore necessary to design a device that would seal various sized external nares and not extend inside the nasal opening far enough to cause mechanical injury to the nasal turbinates or mucous membranes.

A NEWLY DESIGNED DEVICE

The following device was designed for this purpose:

Figure 2 shows the newly designed tip A, contrasted to the conventional insert B. The new tip can be seen to be dome-shaped, with a minimum taper to allow for secretion drainage away from the opening. The greatest circumference is as close to the opening as possible, so that those with large nasal openings will not have to insert the tip too far into the nasal chambers and still have a complete seal. The wall of the inserted portion is made pliable to conform to the contour of the nares. This design capable of occluding the openings permits suction. The conventional tips are not capable of sealing the nares and displacement is not possible.

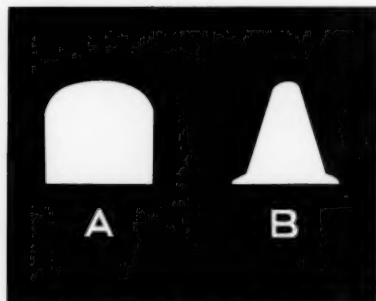


Fig. 2.—Differences between the new and the conventional devices.

This tip fits into a two-ounce plastic squeeze bottle, which is made of a special type of polyethylene that rebounds quickly after being squeezed. This introduces the medication and produces the positive and negative pressure.

EXPERIMENT TO TEST EFFECTIVENESS

In order to determine whether enough pressure was produced to enable the medication to penetrate into the sinuses, the following experiment was performed:

One ounce of 0.25 per cent phenylephrine hydrochloride was placed in the bottle. The patient was instructed to insert this tip into one nostril and press the other nostril closed with a finger. The plastic bottle was squeezed and released three times while the patient continued to say: "Kay, Kay, Kay" during the release. This process was repeated in the other nostril. After the nasal turbinates and sinus openings were shrunk, the procedure was repeated, using Lipiodol.[®] X-rays taken showed the presence of the Lipiodol in the ethmoids (Fig. 3).

The same procedure was followed, using the ordinary squeeze bottle with the ordinary tip and Lipiodol could not be demonstrated in the sinuses.

COMPLICATIONS SOUGHT

Having determined that three squeezes and releases could cause penetration into the sinuses, 200 patients were told to use this method

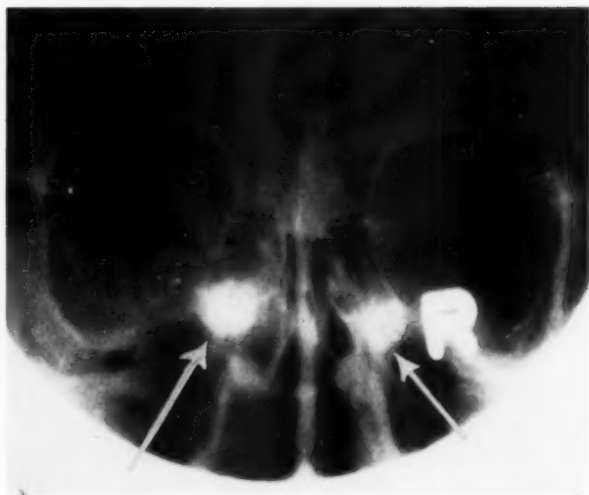


Fig. 3.—X-ray showing lipiodol in ethmoids.

of treatment of their sinuses at home, every 12 hours. Different combinations of drugs were used by the various patients, in order to determine whether the positive and negative pressure produced would cause any harmful effects, such as pushing the infection up the eustachian tube, spreading infection into the sinuses, producing petechial hemorrhages (the latter especially in arteriosclerotic or hypertensive patients), etc. Of the 200 patients listed in Table I (20 of whom had arteriosclerosis and hypertension), not one deleterious effect was noted.

TREATMENT OF THE SINUSES

Sinus treatment is imperative for relief of the bronchial asthma patient, who also has sinus infection.

REPORT OF A CASE

The following case report illustrates this point: J.B.F., aged 57, came in with a history of nasal clogging and bronchial asthma of two years' duration. The asthmatic attacks were brought on by exposure to house dust and by changes of temperature, such as rainy weather. There was no seasonal variation. No past history of allergy. The

TABLE I

NO. OF PATIENTS	DIAGNOSIS	MEDICATIONS USED	COMPLICATIONS OR SIDE EFFECTS
50	Acute infectious Rhinitis & Sinusitis	15 cc Clopane® Hydro- chloride with 10,000 units Penicillin-G per cc	None
50	Allergic Rhinitis and Sinusitis	0.5% Ephedrine in Physiological Saline	None
50	Allergic Rhinitis and Sinusitis	0.25% Phenylephrine Hydro- chloride (Neo Synephrine®)	None
50	Allergic Rhinitis and Sinusitis	Prednisolone Acetate (Metreton®)	None

family history showed bronchial asthma to be present in patient's mother. Urinalysis and blood studies were normal. Physical examination was negative except for blood pressure 180/100. X-ray showed a bilateral ethmoiditis. Intradermal skin tests were positive to house dust, *Staphylococcus Aureus* and *Streptococcus Viridans*.

The patient was given Clopane Hydrochloride® and penicillin drops locally (10,000 units penicillin per cc), was instructed to keep his environment as free from dust as possible, and was given hyposensitization treatments with dust, *Staphylococcus Aureus* and *Streptococcus Viridans*, but he continued to have asthma.

An autogenous vaccine was made from his nasal and pharyngeal membranes. He showed positive skin reactions again to *Staphylococcus Aureus* and *Streptococcus Viridans*, as well as to a gram negative rod. These were added to the hyposensitization treatments, with no diminution of the bronchial asthma.

The patient was then instructed to give himself the continuous sinus suction treatment every 12 hours, using the same Clopane Hydrochloride with Penicillin-G, Crystalline-Potassium 150,000 units to 15 cc Clopane. Within two weeks, his nasal and asthmatic symptoms disappeared and have not recurred for two years.

This same patient had received Clopane with penicillin previously, using them as nose drops with no effect. However, using the same medication with positive and negative pressure enabled the medicines to reach the infected ethmoids and clear them of infection.

SUMMARY AND CONCLUSION

A newly designed, useful, therapeutic device is described, which enables the patient to introduce the proper medicinals directly into the paranasal sinuses, including the ethmoids and sphenoids. Treatment was given by the patient at home, every twelve hours to insure uninterrupted continuous therapy, between visits to the physician. Getting the therapeutic agents into the sinuses is accomplished by the production of positive and negative pressure through the use of an inexpensive, specially constructed, spring polyethylene material that can be discarded when the medication has been exhausted.

Of 200 patients using this treatment at home every 12 hours, no complications occurred, even though 20 of these patients had arteriosclerosis and hypertension.

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XXIX

UNILATERAL HEADACHES OF DENTAL ORIGIN

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ORANGE, N. J.

Because dentists use local anesthesia to pinpoint referred pain, that technique was tried in a differential diagnosis of unilateral headaches of dental origin.

Unilateral headaches can be caused by forcible and sustained contractions of the masticatory muscles. Tunis and Wolff¹ induced headaches by repeatedly contracting the temporal muscle by electric stimulation. Then they injected a local anesthetic into that muscle to promptly relieve the head pain.

Abnormal tooth grinding habits (bruxism) require prolonged and forcible contractions of the masticatory muscles. These incessant, non-purposeful contractions may cause unilateral headaches.² An anesthetic injection (Fig. 1) into these muscles will relieve the headache. When this occurs, the physician may suspect a dental cause. His diagnosis can be confirmed if the headaches do not recur after dental rehabilitation.

REPORT OF TWO CASES

CASE 1. A 46 year old housewife complained to her physician of severe recurrent headaches in the left temporal and suboccipital regions. The headaches began five months ago following the insertion of full upper and partial lower dentures. Neurologic consultation eliminated the central and peripheral nervous systems as the cause of her complaints.

Her dentures were ill-fitting and she gritted her teeth. I advised her to remove the full upper denture for one week; the headaches ceased. Then she wore the dentures daily for a second week. The headaches recurred.

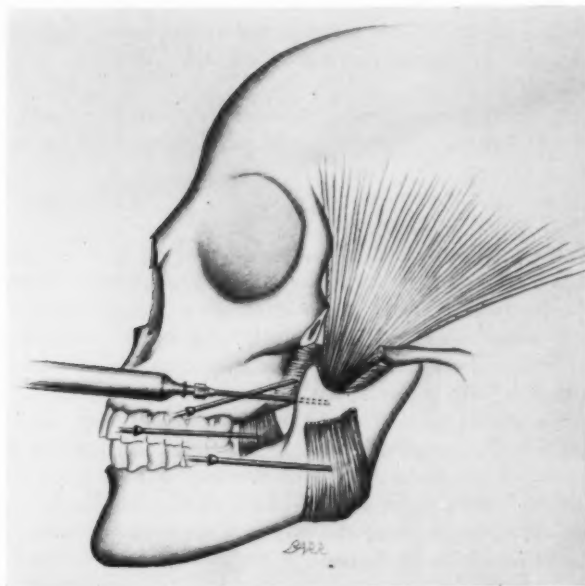


Figure 1

During an attack of severe pain in the left temporal and suboccipital regions, I injected intraorally 2 cc of an anesthetic solution into the four homolateral masticatory muscles (temporal, masseter, internal and external pterygoids). Within three minutes the headache disappeared. Subsequently, her mouth was rehabilitated with new dentures and she stopped the grinding habit. The headaches did not recur and she remains asymptomatic to the present date.

CASE 2. A 48 year old housewife complained to several physicians of repeated headaches in the left temporal, parietal and suboccipital regions. Her headaches started about seven years ago. Only temporary relief was obtained by medication.

She had worn a complete but ill-fitting denture for ten years. Her lower molars and premolars were missing and she gritted her teeth constantly, especially while watching television.

During a painful episode, I injected intraorally 2 cc of a local anesthetic into the four masticatory muscles. The pain diminished

within three minutes and disappeared completely in ten minutes. A few weeks later, her mouth was rehabilitated with a new full upper and a partial lower denture. She stopped the grinding habit and the headaches ceased. She was asymptomatic one year later.

Eight other patients were successfully treated, ranging in age from 21 to 51 years. In a case of malocclusion no relief was obtained.

COMMENT

Sensory fibers located in the periodontal membrane govern the efferent neural impulses to the masticatory muscles.³ When these receptors are overstimulated, as in abnormal grinding habits, a partial tetany of these muscles often results producing pain which may be referred to a homolateral region of the head. An infiltration anesthetic injection into the overactive masticatory muscles eliminates the pain within five minutes. When this is followed by oral rehabilitation that abolishes the grinding habit, the headaches usually do not recur.

Although one patient had a severe malocclusion, he did not grind his teeth. Neither the anesthetic injection nor subsequent oral rehabilitation eliminated his headaches.

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XXX

A SURVEY OF MIDDLE EARS: 101 AUTOPSIES OF INFANTS

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The earliest study of magnitude of the middle ears of infants was done by Aschoff in 1897¹ which included gross examination of the opened tympanic cavities of autopsied infants, followed by histological preparations. Among other aspects, Aschoff was concerned with amnionic debris within the middle ear cavities. The next major works of a similar nature were performed by Wittmaack in 1918 and in 1926² in which he proposed that irregularities of the mastoid air spaces represented abnormal development, and that pathological types of mucosa influenced the susceptibility to otitis media.

In 1940 Diamant³ demonstrated normal variation in size and distribution of mastoid air spaces in the general population by use of planimetric measurements on roentgen pictures taken partly of normal mastoids and partly of instances of chronic otitis media.

In 1948 Diamant and Lilja⁴ reported a series of patients in which pre-operative roentgenography was correlated with histological studies of mastoidectomy bone chips.

Material obtained from 375 mastoidectomies were studied by Friedmann in 1956⁵ from which he concluded that no evidence existed which would indicate that the basic pathology of otitis media had changed in the post-penicillin era; that the mucosa of the ear is very susceptible to infection, and that the hyperplastic mucosa and osteoplastic processes which were observed were the result, rather than the predisposing factor, of otitis media. Studies of temporal bone infections in the antibiotic era have been reported by various investigators.⁶⁻⁹

In 1953, Werne and Garrow reported a large series of necropsies of infants dying in various circumstances. Their series included infants "found dead,"¹¹ infants observed to die suddenly,¹² and those

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dying immediately after trauma.¹³ All viscera were carefully examined, including sections from the mastoids in most instances. They found that mastoiditis occurred in a high percentage of infants dying from infections as evidenced by inflammatory changes in viscera and by bacterial cultures.

The complications of otitis media were reviewed by Dysart in 1959,¹⁰ which included other organs than the middle ears.

In 1955 Wilson indicated that true mastoiditis exists only after development of the mastoid air cells, which should be completed by the fifth year of life.¹⁴

In 1960, McLellan and Stout reported otitis media in a premature infant and indicated that this is considered to be an uncommon finding. They also stated that this was the first such instance that they had observed.¹⁵

Thus, the correlation of inflammatory changes in the temporal bone, including middle ears and mastoids, with findings in other organs has long been recognized as existing, and has received careful scrutiny in certain medical and scientific centers. However, this correlation, and the implications thereof, are not always accorded the attention deserved. This survey is a study of such relationships in detail.

The sources of material in this series include autopsies on infants up to two years of age dying at the John Gaston Hospital, or dead upon arrival here, as well as autopsies at Le Bonheur Children's Hospital between July 1, 1957 and July 1, 1960. One of the infants was a stillborn which was added because of the severe otitis media present bilaterally (Fig. 3). We have examined the middle ears in 36 other stillborns at various stages of development, and with various maternal complications. In none of these was there definite evidence of inflammation. In a few instances there were slight hemorrhages.

All the structures of the middle ears, as well as the inner ears, were removed in a single block on each side. Using a stryker electric saw, four cuts were made. The midial cut was made longitudinally with the anterior-posterior axis of the skull, extending from the jugular foramen across the petrous ridge to the area of the foramen lacerum, preserving the basilar portion of the occipital bone, and the bony formation of the foramen magnum. The posterior cut extended from the region of the jugular foramen lateralward, and slightly backward, to the lateral border of the posterior fossa, including the petrous portion of the temporal bone, as well as the superior petrosal sinus. The

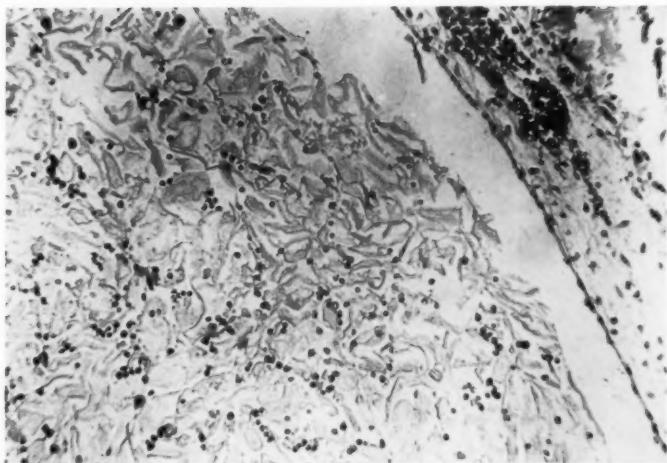


Fig. 1.—Infant 4, Squame cells filling middle ear cavity with scattered inflammatory cells. Case of abruptio placenta. Many squame cells in pulmonary alveoli. Magnification 100.



Fig. 2.—Infant 57, Early acute otitis media. Pink, homogenous material filling tympanic cavity. Few inflammatory cells, Gram positive cocci and Gram negative rods present. Magnification 17.5.



Fig. 3.—Infant 22, Purulent otitis media in stillborn. Congenital hydrocephalus with cranial puncture necessary for delivery. Second stage of labor one hour and twenty minutes. Note ear drum and external canal in lower corner of photo. Magnification 100.

lateral cut began at this point in the posterior cranial fossa, just within the wall of the fossa, extending forward across the petrosal ridge into the middle fossa, ending within the squamous portion of the temporal bone. The most anterior cut joined the medial and lateral cuts, and is the cut most likely to exclude the anterior parts of the middle ears. This is true because in infants, the middle ear cavities are anterior. These four cuts leave loose fibrous attachments in the deeper portions, which can be easily severed by long, curved scissors. This roughly square portion of the temporal bone includes the inner ear structures, the tympanic cavity with the ossicles, the innermost portion of the external auditory meatus and its termination at the tympanic membrane, as well as a portion of the mastoid bone, depending upon the stage of development.³

Sections were made parallel with the external auditory meatus, in a vertical plane, so as to include the tympanic membrane. In many instances, the attachment of the malleus to the drum was present on at least one section from each ear (Fig. 10). Multiple sections, stained by hematoxylin and eosin, periodic acid Schiff, and Gram's stain, were studied from each middle ear.

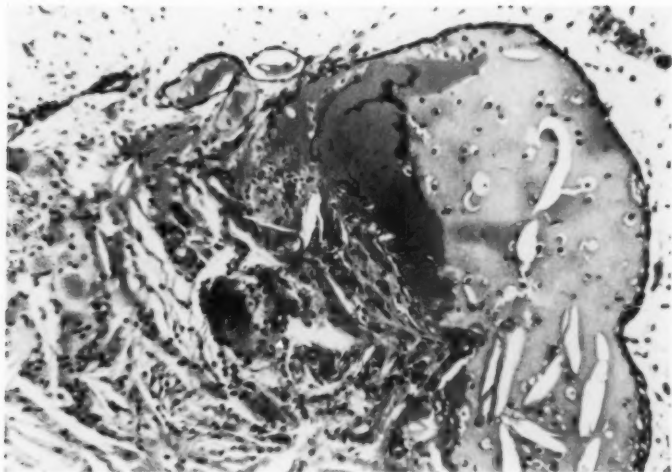


Fig. 4.—Infant 2, Acute and chronic otitis media. Note homogenous material with scattered inflammatory cells, and some irregular spaces, which is continuous with the granulation tissue. The latter consists of many capillaries, mononuclear cells, fibroblasts, and 'cholesterol-like' clefts. Magnification 100.

The criteria used for classification of otitis media, as well as otitis interna and otitis externa, in these infants correspond with those used generally by pathologists for any tissues. Each instance of inflammatory change of the middle ear, the inner ear, and the external ear canal was placed in one of three categories. These were acute, sub-acute and chronic, with a qualifying adjective, such as hemorrhagic, minimal, exudative, or with granulation tissue.

In those instances in which considerable amounts of a pink, protein-like material were observed filling the middle ear cavities, with only a few, scattered neutrophils within this material (Fig. 2), examination of the mucosa revealed at least a few inflammatory foci. These findings probably represent what is clinically referred to as "serous otitis media,"¹⁶ as "secretory otitis media,"¹⁷ and has frequently been labeled "non-suppurative," being described as "otitis media with sterile effusion" by Hoople, 1905. This entity was said to have increased in clinical incidence between 1950 and 1955.¹⁷ Middle ears revealing the preceding morphological changes are herein labeled acute otitis media. In other instances, there were little or no protein-like

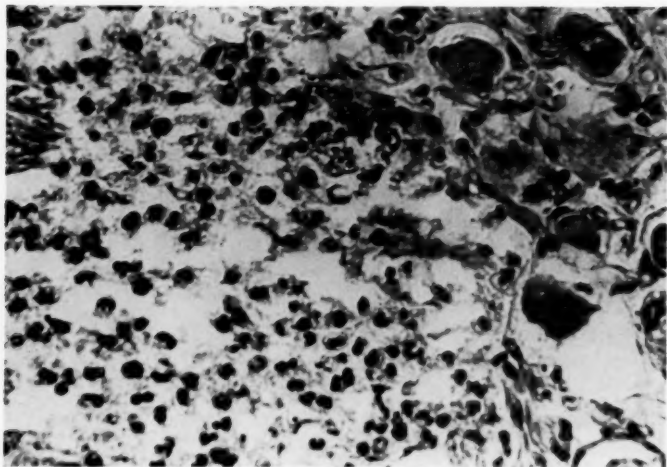


Fig. 5.—Infant 13, Acute otitis interna. Note large ganglion cells of cochlear division of VIII nerve. Magnification 200.

material present with varying amounts of pus within the tympanic cavity. Mucosal inflammatory changes were present in each. Combined variations of these changes have been labeled acute otitis media in this series.

In the middle ears of some of the infants examined, a large amount of exudate filled all air spaces with only a mild epithelial change. In still others, a marked mucosal alteration existed without any striking exudation. It was considered that the latter type probably represented a more chronic process.

Another frequent finding of interest was minimal inflammatory change in the tympanic membrane, other than severe vascular congestion, in the presence of severe otitis media. The capillary dilatation of the drum may account for most of the red color observed clinically in such instances. This particular change was present in acute and chronic otitis media.

A finding of apparent incongruity was the difficulty in finding bacteria on Gram's stains in a few infants with purulent otitis media. Also, there was a small number in which the predominant inflamma-

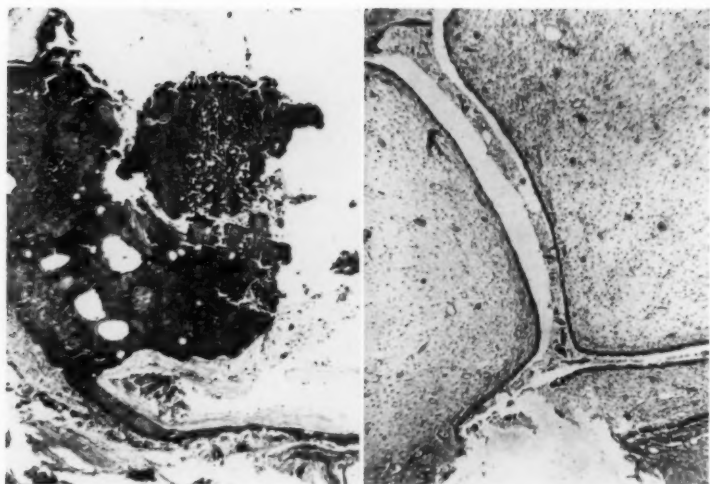


Fig. 6.—Infant 3, Otitis externa. Mass of necrotic, keratotic material protruding into external canal near drum. Note mass arising from stratified squamous epithelium. Magnification 17.5.

Fig. 7.—Infant 68, Edema-like thickening of middle ear mucosa. Congenital underdevelopment? (See Figure 8.) Magnification 17.5.

tory reaction was of the mucosal epithelium without demonstration of organisms. Both of these groups combined, however, constituted a small minority, with the majority having easily demonstrable organisms. Usually both gram negative rods and gram positive cocci were present. In thick exudates, bacteria were often seen only at the margin of the exudate, in the thinnest portions.

Subacute otitis media is used herein with reference to those instances in which an element of acute inflammation was present, frequently a few eosinophils, plus evidence that the inflammatory changes had existed for some time, such as focal collections of lymphocytes in the subepithelium, and the absence of definitely chronic inflammation. Many of those labeled subacute had focal mucosal involvement, without exudate or transudate demonstrated in the tympanic cavities. Some of these contained a high per cent of lymphocytes in the submucosa, and the distinction from a low grade, chronic otitis was difficult.

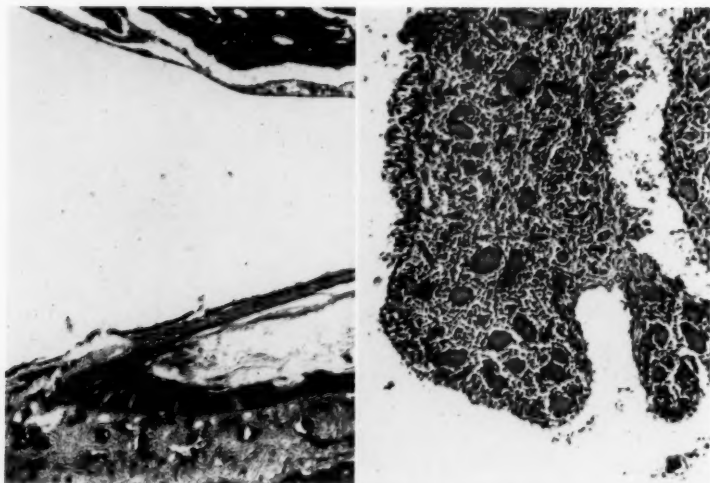


Fig. 8.—Infant 29, Normal tympanic cavity. Large space is tympanic cavity with normal, thin mucosa and sub-mucosa in infant dying of cerebral hemorrhage. Thin partition is ear drum with external canal also shown. (See Figure 7.) Magnification 17.5.

Fig. 9.—Infant 21, Chronic otitis media. Note vascular dilatation. Cardiac massage during abdominal surgery. Magnification 100.

In immature infants, the distinction between foci of submucosal hematopoiesis and focal areas of inflammatory reaction was made by the following criteria, with the use of Giemsa stains. Hematopoietic foci tend to be perivascular; some distance below the epithelial lining cells; a variety of cell types with increased nucleated red cells; widely scattered in the mesenchymal tissues if not around blood vessels; higher in percentage of various stages of maturity of eosinophils. In contrast, in focal chronic, or subacute otitis media, the cells in question tend to be in juxtaposition with the epithelium; chiefly of a single cell type, usually lymphocytic; and densely packed rather than diffusely scattered.

A second, somewhat similar problem in immature infants was encountered in those instances interpreted as being residual, and probably healing otitis media, but presumably the source of infection of other organ systems; an alternate pathogenesis being that the infant was merely made more susceptible to any infection because of the



Fig. 10.—Infant 2, Attachment of malleous to tympanic membrane. Purulent exudate is present within middle ear cavity. Magnification 100.

healing, or chronic otitis media. Another possibility is that the infant's total resistance was lowered for undetermined reasons, both as to middle ears as well as other body systems. An example of the latter possibility was a four day old immature infant, Infant 1, who had conjunctivitis. This responded to therapy, but the infant continued to have a slight fever of undetermined origin and developed sclerema neonatorum. He then developed pneumonia and expired. That the middle ears constituted the basis of the fever, and possibly the sclerema neonatorum and pneumonia was shown by the marked, chronic and acute otitis media, bilateral, found at necropsy.

There were two infants with otitis externa. One of these, Infant 2, also had meningitis and bilateral acute otitis media. The other, Infant 3, had septicemia, acute gastro-enteritis, and otitis media. In both, elevated masses of necrotic, eosinophilic material were attached to and continuous with the stratified squamous epithelium of the auditory canal near the tympanic ring (Fig. 6).

SQUAME CELLS

The importance of amnionic debris within the tympanic cavities was studied by investigators before the turn of the century. In the present series, only two infants were found to have large numbers of squame cells within the middle ear spaces. One of these, Infant 4, was a full term infant whose birth was complicated by an abruptio placenta, living only one day. At necropsy the lungs were filled with amnionic debris without pneumonia. In the tympanic cavities there were many squame cells, among which were numerous neutrophils, as well as gram positive cocc (Fig. 1). On the basis of these findings, the diagnosis of acute otitis media was made. The other, Infant 5, a four day old immature infant, also was associated with an abruptio placenta. There were large numbers of squame cells within the tympanic cavity of one side; the other middle ear cavity being clear. It is of interest that an acute exudative otitis media was present in the middle ear containing the amnionic debris, but not in the opposite ear. Bronchopneumonia was also present.

DEHYDRATION AND MALNUTRITION

Three deaths were considered to have been primarily due to this syndrome, Infants 6, 7, 8. Infant 6, clinically considered to have brain damage, had acute and chronic otitis media bilaterally, expiring when two months old. Gram positive cocci were present in the middle ear exudates. Infant 7 was a "dead-on-arrival" without much available clinical data, other than a vague history of diarrhea. The infant was severely dehydrated and mal-nourished, and had severe excoriations of the buttocks. The middle ears revealed acute and chronic otitis, with granulation tissue formation, including multinucleated giant cells, and myriads of gram positive cocci in clumps and short chains in the exudate. Fungus stains were negative. Infant 8 was full-term who suffered recurrent diarrhea with resultant dehydration and malnutrition, dying at four weeks. A monilia infection of the dorsum of the tongue was present at necropsy, as well as acute and chronic otitis media with marked mucosal edema and exudate. In the latter, gram positive cocci were present in the middle ear exudate.

OTITIS INTERNA AND MENINGITIS

Although the original objective was primarily to study the middle ear spaces, sections have included the inner ear structures also, and thus were easily studied. In three infants, otitis interna was present

(Fig. 5), all associated with meningitis. Of these three, one also had otitis media bilaterally. Of the six instances of meningitis in the series, two did not have otitis media, both being cases of otitis interna.

CONGENITAL MALFORMATIONS

Fourteen infants came to necropsy in which a malformation, or malformations, was considered the major disease process; however, in nine of these there was an infective, or inflammatory process which was considered in most instances to be the terminal factor. Seven of these nine also had an otitis media (Fig. 9). Five anomalies, multiple in some instances, were so severe as to be lethal per se. Tables II and III summarize these 14 cases.

TABLE I
MENINGITIS AND OTITIS

INFANT NUMBER	ETIOL. AGENT	AGE	MIDDLE EARS	INNER EARS	EXTERNAL AUDITORY CANAL
2 A58-1164	H. Influenza	4 months	Acute and chronic otitis. Granulation tissue. Coccobacillus, gram positive	Negative	Kerato-fibrino-necrotic exudate
9 A58-966	Streptococci	3 weeks	Purulent exudate. Gram positive rods with terminal spores	Negative	Negative
10 A58-475	Streptococci	1.5 months	Acute otitis, slight, bilateral. Gram positive cocci	Purulent otitis; Gram pos. cocci	Negative
11 A60-131	No cultures; Mixed organisms on Gram stains	10 days	Negative	Acute and chronic. Many Gram positive cocci & neg. rods	Negative
12 A59-932	Streptococci	6 months	Sub-acute, mild bilateral	Negative	Negative
13 A58-1170	Not cultured Gram negative rods, positive cocci in pairs Probably pneumonocci	9 months	Negative	Hemorrhagic otitis, 8th nerve involved. Gram neg. rods. Positive cocci in pairs	Negative

TABLE II
CONGENITAL ANOMALIES WITH INFECTION

INFANT NUMBER	AGE	MALFORMATION	INFECTIVE PROCESS	MIDDLE EARS
14 A59-327	1 month	Multiple: Eisenmenger's, hair-lip and cleft palate; extra digit; undescended testes	Bronchopneu- monia	Negative
15 A59-30	2 weeks	Hirschsprung's disease - (operated) acidosis devel- oped 3 days postoperative	Dermal ulcer of leg with terminal sepsis. Staphylo- coccus in blood culture	Sub-acute oti- tis bilateral
16 A57-822	5 days	Congenital laryngeal stri- dor: Proven by laryn- gocopy	Bronchopneu- monia with sec- ondary paralytic ileus	Acute, suppu- rative otitis, bilateral gram pos. cocci, sin- gle, pairs and short chains
17 A59-414	7 months	Endocardial fibroelastosis	Interstitial pneu- monia	Acute & sub- acute otitis bi- lateral. Gram pos. cocci in clumps
18 A58-501	2 days	Posterior urethral valves, "A,B,O," blood incom- patibility. (Expired dur- ing transfusion)	Pyelonephritis, mild unilateral	Negative
19 A58-295	1.5 months	Endocardial fibroelastosis	Interstitial pneu- monia	Acute otitis bilateral, non- purulent "ser- ous" type
20 A58-491	4 days	Multiple: Renal agenesis- left; hypoplastic, poly- cystic rt. kidney; micro- agnathia; marked epi- canthal folds	Bronchopneu- monia	Sub-acute oti- tis, bilateral
21 A58-1226	2 months	Fibrous band across colon at spleen (cardiac arrest during surgery)	Pathogenic E. coli (0126:B16) - recurrent diarrhea	Severe acute & sub-acute oti- tis, bilat. Gram neg. rods
22 A58-944	Still- born	Hydrocephalus 1,000 ml. cerebrospinal fluid removed before delivery	Slight chronic inflammation of arachnoid around 4th ventricle	Acute exuda- tive otitis, bi- lateral. Gram pos. cocci in pairs, single & short chains, pos. rods

TABLE III
CONGENITAL ANOMALIES WITHOUT INFECTION
(OTHER THAN OTITIS)

INFANT NUMBER	AGE	MALFORMATION	INFECTIVE PROCESS	MIDDLE EARS
23 A60-17	1 hour	Multiple: Absence of left diaphragm; others	None	Focal sub-epithelial hemorrhages
24 A59-152	1 month	Tri-cuspid stenosis and focal myocardial calcification	None	Slight acute & sub-acute otitis bilateral
25 A58-642	4 days	Intra-ventricular septal defect	None	Negative
26 A59-101	3 days	Multiple cardiac anomalies	None	Negative
27 A58-638	12 days	Coarctation of aorta	None	Exudative otitis media, right; marked submucosal edema bilateral. Gram pos. cocci and neg. rods

PULMONARY HYALINE MEMBRANES

Of the 13 autopsies revealing this entity, two also revealed an infective process. Ten of the 13 did not have otitis media; one had no other findings than pulmonary hyaline membrane and otitis media; the remaining two had pulmonary hyaline membranes and an infective process other than otitis. Of the last two, one did not have otitis. However, this last one was associated with a placenta previa and massive postnatal aspiration, rather than a truly infective process. Pertinent data of the 13 autopsies with pulmonary hyaline membranes are summarized in Table IV.

BRONCHOPNEUMONIA

There were 22 necropsies which revealed bronchopneumonia with or without other inflammatory processes. In some of these, a second pathological process existed of such magnitude that in the absence of pneumonia, death would have readily attributed to the other process. However, in all 22 the pneumonia was severe enough to have caused death. In only one instance was there absence of an inflammatory

TABLE IV
PULMONARY HYALINE MEMBRANE CHANGES

INFANT NUMBER	AGE	OTHER LESIONS	MIDDLE EARS
28 A59-611	1 day	None	Negative
29 A57-1035	36 hours	Intraventricular cerebral hemorrhage, unilateral	Negative
30 A58-71	2 days	None	Negative
31 A58-943	16 hours	None	Negative
32 A58-570	1 day	Intraventricular cerebral hemorrhage, bilateral	Negative
33 A60-97	23 hours	Aspiration of amnionic debris, moderate	Negative
34 A58-596	1 day	Focal pulmonary hemor- rhages	Negative
35 A58-655	10 hours	None	Negative
36 A58-921	14 hours	None	Negative
37 A58-780	1 day	None	Focal subepithelial hemor- rhages
38 A57-945	5 hours	Intraventricular cerebral hemorrhage, left	Acute, exudative otitis media, bilateral
39 A60-221	10 hours	Bronchopneumonia, bilateral, early (probably aspiratory)	Negative
40 A59-450	18 hours	Bronchopneumonia, bilateral, aspiration	Acute otitis media, bilateral: Small amount of exudate; marked subepithelia inflamma- tion; Gram pos. cocci in chains, and Gram negative rods

process in any of the middle ear structures. Nor did any other organ system than the lungs in this case reveal pathological changes. Table V lists the cases of bronchopneumonia.

SEPTICEMIA

Of the seven deaths due to septicemia, only one did not reveal middle ear inflammatory changes. This infant had omphalitis with

TABLE V
BRONCHOPNEUMONIA

INFANT NUMBER	AGE	DEGREE OF PNEUMONIA	OTHER LESIONS	MIDDLE EARS
41 A59-22	3 months	Bilateral, lower lobes, acute	Malnutrition and dehydration	Sub-acute & exudative acute otitis bilateral. Gram pos. cocci in pairs
42 A59-248	2 months	Bilateral, marked. ate	Perifollicular sple- nic hemorrhages: A-S hemoglobin on paper electro- phoresis	Exudative otitis bilat- eral. Gram pos. cocci, single and in pairs
43 A59-317	10 months	Bilateral, marked: History of recent pertussis	Dehydration	Chronic & exudative acute otitis bilateral. Gram negative rods
44 A58-543	3 weeks	Bilateral, early focal hemorrhage	Monilia, dorsum of tongue	Sub-acute, focal otitis, bilateral
45 A58-207	3 days	Confluent with abscesses, bilateral	None	Negative
46 A58-727	8 months	Bilateral, absces- ses, emphyema	Cutaneous ab- scesses	Acute & chronic otitis, Gram pos. cocci in clumps
1 A60-165	4 days	Bilateral, severe	Sclerema; esoph- agitis; pul. hyal. mem.; conjunc- tivitis	Acute and marked chronic otitis; bilateral
47 A60-122	3 weeks	Bilateral, ab- scesses	Septicemia; clin- ical	Severe acute & chronic otitis, bilateral, Gram pos. cocci & neg. rods
48 A59-145	2 years	Bilateral, marked	Generalized cyto- megalic inclusion disease	Severe acute & chronic otitis, bilateral; Gram pos. cocci & neg. rods
5 A58-486	4 days	Bilateral, hemor- rhagic	Cerebral hemor- rhage, incompl. rotation of gut	Acute, exudative otitis, unilateral. Many Gram neg. rods
49 A58-662	16 days	Bilateral, ab- scesses	Ulcerative esoph- agitis	Acute and chronic oti- tis, bilateral, Gram pos. cocci and negative rods
51 A58-1101	2 months	Bilateral, con- fluent	Renal cytomeg- alic inclusions	Acute, exudative otitis bilateral. Many Gram pos. cocci and neg. rods

TABLE V (Continued)

BRONCHOPNEUMONIA

INFANT NUMBER	AGE	DEGREE OF PNEUMONIA	OTHER LESIONS	MIDDLE EARS
52 A58-29	10 days	Bilateral, ab- scesses	Ulcerative esoph- agitis	Acute & subacute oti- tis, bilateral. Many Gram neg. rods; few Gram pos. cocci
53 A58-1198	7 days	Bilateral, acute	Cerebral hemor- rhage; parotitis; cut. abscesses	Acute, exudative otitis bilateral. Few Gram pos. cocci, singly and in pairs
54 A58-4	12 days	Bilateral, marked	Ulcers, dorsum of tongue	Severe acute and sub- acute otitis. Few Gram neg. rods
55 A59-804	9 days	Bilateral, ab- scesses	Septicemia: Sta- phylococcus aure- us, coag. positive	Acute, exudative otitis bilateral. Many Gram neg. rods
56 A57-784	4 months	Bilateral, early	Tracheitis	Acute and sub-acute otitis, bilateral, Gram negative rods
57 A60-155	3.5 months	Bilateral, marked	Abscesses of face and scalp	Sub-acute and chronic inflammation of muco- sa, bilateral with pro- tein exudate and neu- trophils. Gram pos. cocci and neg. rods
58 A57-848	2 months	Bilateral, ab- scesses	Monilia, tongue; abscesses of but- tocks	Exudative otitis bilat- eral
59 A59-970	7 months	Bilateral, moder- ate sub-acute	Septicemia; fatty liver, malnut., dehydration	Chronic otitis, bilateral with focal squamous metaplasia. Gram neg. rods
60 A58-707	1 day	Bilateral, slight	None	Mild, acute otitis, bilateral
61 A58-1217	3 months	Bilateral, confluent	None	Acute and chronic oti- tis media, bilateral. Gram pos. cocci

TABLE VI
SEPTICEMIA AS THE CHIEF PATHOLOGICAL PROCESS

INFANT NUMBER	AGE	EVIDENCE OF SEPSIS	OTHER LESIONS	MIDDLE EARS
62 A59-70	19 days	Autopsy cultures: Hemolytic staphylo- coccus aureus	Omphalitis; broncho- pneumonia, aspiration	Negative
63 A58-104	12 days	Adrenal hemorrhages; pul. hemorrhages; esophagitis; hemolytic staphylococcus aureus; fatty metamor.-liver	—	Otitis media, mild Gram pos. cocci bilat- eral
3 A59-952	4 months	General infection: Gastro-enteritis; hepa- titis, pericarditis	Dehydration	Chronic and acute exu- dative otitis media, with granulation tis- sue; otitis externa
64 A59-372	4 months	Postmortem blood cul- tures: Staphylococcus aureus, coagulase pos.	None	Acute, exudative otitis media, bilateral
65 A58-52	1 month	General infection: Jaundice; meningitis; bronchopneumonia	—	Exudative otitis media, bilateral Gram pos. cocci and neg. rods
66 A58-130	Unkn'wn, Dead on Arrival; 45 cm, 1850 gm	General infection: omphalitis; focal, ulcer, enteritis; hep- atic necrosis; broncho- pneumonia	Ectopic kidney	Exudative otitis media, bilateral, Gram pos. cocci
67 A59-826	1 month	Autopsy cultures of blood: Pseudomonas aerogenosa	Interstitial pneumonia	Acute and sub-acute otitis media bilateral, Gram neg. rods and pos. cocci

a resultant sepsis. It is difficult to explain why otitis media did not exist. Two of the seven also had enteritis, which was probably the source of the blood stream infection. The middle ears of one infant with septicemia revealed chronic otitis media with cholesterol-like spaces (Fig. 4). The seven necropsies of infants with septicemia are summarized in Table VI.

INTERSTITIAL PNEUMONIA

Of the five infants with interstitial pneumonia, three also had otitis media. Since it has been shown that bacteria as well as bacterial

TABLE VII
INTERSTITIAL PNEUMONIA

INFANT NUMBER	AGE	OTHER LESIONS	MIDDLE EARS
68 A59-924	27 days	Idiopathic cardiac hypertrophy, omphalitis	Marked edema-like thickening of the sub-epithelium
69 A58-2	3 days	None	Exudative otitis media, bilateral, Gram positive cocci
70 A58-1292	3 weeks	Fatty liver	Exudative otitis media, bilateral, Gram positive diplococci - resembling pneumococci and few Gram negative rods
71 A59-7	6 months	Focal, acute pancreatitis	Exudative otitis media, bilateral, with protein material in cavity and Gram positive cocci in short chains and Gram negative rods; inflamm. cells in sub-epithelial tissues
72 A58-1043	6 days	Dilatation of extra hepatic bile ducts, etiology unknown	Negative

TABLE VIII
LEUKEMIA AND OTITIS MEDIA

INFANT NUMBER	AGE	MAJOR PATHO- LOGICAL PROCESS	MIDDLE EARS
73 A60-271	1 month	Acute Leukemia	Focal hematopoiesis, areas of sub-acute and chronic otitis; red cells sickled
74 A59-1072	4.5 months	Acute, granulocytic leukemia	Leukemic infiltrate mucous membranes; acute and chronic otitis media, bilateral; exudative

toxins alone can result in an interstitial pulmonary reaction,¹⁸ it is not surprising that purulent otitis media of bacterial etiology very frequently accompanies institial as well as bronchopneumonia. Of the two without otitis, one had an idiopathic cardiac hypertrophy, and a marked reduction of the tympanic cavity volume. This was due to a marked edema-like thickening of the subepithelial tissues (Fig. 7). Although this infant was premature, 1,115 grams, 37.5 cm crown-heel length, and slightly over six months gestation, and only 27 days of age

TABLE IX
INTRA-UTERINE PNEUMONIA

INFANT NUMBER	AGE	MATURITY	MAJOR DISEASE PROCESS	ASSOCIATED FACTORS	MIDDLE EARS
81 A59-358	2 hours 43 min.	Immaturity, 533 grams, 30 cm crown- heel length	Intra-uterine pneumonia, bi- lateral, marked	Fetal mem- branes rup- tured, 48 hours	Suppurative oti- tis media, bilat- eral; squame cells present; few Gram neg. rods
82 A58-689	6 hours	Immaturity, 910 grams, 34 cm crown- heel length	Intra-uterine pneumonia, bi- lateral, marked; extensive aspir- ated debris; ate- lectasis; intra- ventricular cere- bral hemorrhage	Prolapsed umbilical cord, one hour	Negative
83 A58-683	6 hours	Prematurity, 1,000 grams, 39 cm crown- heel length	Marked aspira- tion of amnion- ic debris; intra- uterine pneu- monia, bilateral	Fetal mem- branes rup- tured, 4 days	Suppurative oti- tis media, bilat- eral; Gram neg- ative rods and positive cocci present
84 A58-672	2 days	Prematurity, 1,400 grams, 40 cm crown- heel length	Marked aspira- tion of amnion- ic debris; early intra-uterine pneumonia, bilateral	Placenta previa and cesarean section	Negative

when expiring, this does not represent a stage of development consistent with this gestation age (Fig. 8). This morphological finding has not been present in the middle ears in any other corresponding age. It more closely resembles the normal finding in fetuses of three to four months gestation. Whether this represents a retardation of development of the middle ears, and hence, a congenital anomaly, or edema secondary to cardiac failure, or other causes, is uncertain. The first possibility appears more attractive, inasmuch as other cases of lethal cardiac malformations have not shown any such edematous changes in this location.

LEUKEMIA

The two infants with leukemia had bilateral otitis media. This interpretation was based upon the same criteria as in other cases.

TABLE X
FATAL HEMORRHAGE IN THE NEWBORN

INFANT NUMBER	AGE	SITE OF HEMORRHAGE/s	OTHER LESIONS	MIDDLE EARS
85 A58-861	8 days	Pulmonary, multiple; cerebral	Omphalitis; heal- ing pyoderma	Focal hemat- opoiesis; in- fant imma- ture
86 A58-470	2 days	Cerebral; pulmonary	Sclerema neona- torum	Exudative otitis, Gram pos. cocci in chains
87 A60-85	2 days	Pulmonary	None	Negative
88 A59-333	3 hours	Multiple organs	None	Focal hemat- opoiesis; in- fant prema- ture
89 A58-978	20 minutes	Multiple organs: Clinical history of prolapsed um- bilical cord	Hyperplasia - islets of Langer- han and cardiac hypertrophy; ma- ternal diabetes; liver: Riedel lobe and hemangioma	Negative
90 A59-989	8 hours	Hemothorax; hemopericar- dium sub-arachnoid, focal; petechiae - many; abruptio and marginal sinus throm. of placenta	Ascites, 20 ml	Vascular congestion
91 A58-674	4 hours	Pulmonary; conjunctive; liver: sub-capsular, twin No. 2, double footling	Multiple cysts, adrenal cortices	Vascular congestion
92 A58-1263	2 days	Pulmonary, multiple	None	Focal hemat- opoiesis, in- fant prema- ture

However, it should be noted that in Infant 73 there were foci of hematopoiesis some distance away from the epithelial lining cells of the tympanic cavities. The second, Infant 74, survived until 4.5 months of age. While this infant had leukemic infiltrate in the tympanic epithelium, the middle ear cavities were filled with pus; hence, was considered purulent otitis media. The reduced resistance

TABLE XI
BIRTH TRAUMA (KNOWN CLINICALLY OR EVIDENT AT AUTOPSY)

INFANT NUMBER	AGE	SITE OF TRAUMA	MECHANISM
93 A59-403	2 days	Cerebral hemorrhage	Breech delivery
94 A58-663	5 days	Vein of Galen ruptured: posterior fossa hemorrhage	Twinning with difficult delivery
95 A59-132	1 day	Ruptured right internal cerebral vein: subdural hemorrhage	Unknown
96 A58-1281	8 minutes	Severe vascular congestion, all organs; ependymogial hemorrhages	Prolapsed umbilical cord with version and extraction

to infections in general, common to the leukemias, appears probably to apply equally well to the tympanic cavities.

PRIMARY ATELECTASIS

Six infants, Infants 75 through 80, which expired very shortly after delivery, had no finding other than lack of pulmonary expansion. In none of these were inflammatory phenomena of the tympanic cavities present.

INTRA-UTERINE PNEUMONIA

Four newborn infants were considered to have pneumonia of intra-uterine origin. This diagnosis was based, in each case, upon several factors, not all of which were necessarily present, among which were: death within a few hours after birth; clinical evidence of respiratory distress from delivery; evidence of amnionitis, either clinical, or acute inflammation of the umbilical cord; or a history of membranes rupturing several days before delivery; absence of focal pulmonary necrosis, although this is not an absolute criterion; but is more common in post delivery aspiration; generally, a diffuse, or uniform pneumonia rather than a lobular or bronchopneumonia. However, this latter feature is not an absolute criterion, as known cases of stillbirths in the John Gaston Hospital have been found to have a very focal, widely scattered pneumonia.

Of the four infants with intra-uterine pneumonia, two had an acute, bilateral otitis media. One of these, Infant 81, lived two hours

TABLE XII
MISCELLANEOUS

INFANT NUMBER	AGE	MAJOR DISEASE PROCESS	MIDDLE EARS
97 A58-200	2 weeks	Omphalitis; peritonitis; septicemia. (Staphylococcus aureus, coagulase positive, post-mortem cultures)	Acute and chronic otitis media; Gram positive cocci in clumps
98 A59-583	6 weeks	Spinal nuclear amyotrophy (Werdnig-Hofmann's syndrome); bronchopneumonia, early	Acute otitis media, bilateral, Gram stains negative
99 A58-623	1 hour	Anasarca, etiology unknown; calcification of aorta, pulmonary and splenic arteries	Middle ears negative
100 A57-932	17 days Immature 950 grams 40 cm crown-heel length	Intra-ventricular cerebral hemorrhage; aspiration of gastric contents	Suppurative otitis media, bilateral; many Gram negative rods present
101 A58-724	2 days	Erythroblastosis fetalis; (positive coomb's test: Infant A, mother O blood types)	Negative

and forty-three minutes; the other, Infant 83, lived six hours and revealed massive aspiration of amnionic debris. Of the two infants without otitis media, one, Infant 82, lived six hours having a prolapsed umbilical cord and an intraventricular cerebral hemorrhage. The second infant without otitis media, Infant 84, lived two days and was associated with a *placenta previa* and Cesarean section.

NEO-NATAL HEMORRHAGES

Eight deaths in newborn infants were attributed to hemorrhage. The age range was from 20 minutes to eight days. However, two of the eight are of questionable validity in this classification. One of these, Infant 85, had omphalitis, pyoderma and probably septicemia. The other infant, Infant 86, had sclerema neonatorum with bilateral purulent otitis media the only infective process present at necropsy. The relationship between the severe middle ear infection and sclerema in this instance is not proven, but is highly suggestive.

BIRTH TRAUMA

Known clinically or evident at autopsy. There were four such infants, all dying fairly soon after delivery. The chief interest in these was the absence of inflammatory changes in any organ, and correspondingly negative findings in the middle ears. The survival for five days by one, Infant 94, with a posterior fossa hemorrhage is unusually long.

PERITONITIS

One full-term infant, Infant 97, who lived two weeks had peritonitis as the basic disease process with an infected umbilical stump as the probable portal of bacterial entry. Peritonitis developed fairly early as was proven by paracentesis in the first week of life. Secondary septicemia developed with focal liver necroses and esophagitis. She also suffered from diarrhea. Hemolytic staphylococcus, coagulase positive was cultured, post mortem from the peritoneum and esophagus. The umbilicus revealed marked acute and chronic inflammation. Acute and chronic otitis media, bilaterally, were present with Gram positive cocci in clumps present in the exudate.

MISCELLANEOUS

The only inflammatory lesion present in one infant with Wernig-Hoffmann's disease, Infant 98, was subacute otitis media, bilaterally. This full-term infant lived six weeks and expired from the marked central nervous system lesions including the brain stem. No organisms were found on Gram stains of the middle ears.

One premature infant who lived one hour, Infant 99, had generalized severe pitting edema, etiology undetermined. The middle ears were negative.

One premature, seventeen day old infant expired because of massive aspiration of food, Infant 100. There was a recent intraventricular hemorrhage considered secondary to hypoxia. The middle ear cavities revealed an exudative inflammation, with many Gram negative rods in the exudate, but no inflammatory changes in other organs. An alternate possibility exists that the cerebral bleeding preceded the aspiration, as occurs in the aged patient. In any event, the otitis media undoubtedly existed prior to the aspiration.

One fatal instance of erythroblastosis fetalis, Infant 101, autopsied in this series had no inflammatory process in any organ, other than hematopoiesis, and had no middle ear inflammation.

TABLE XIII
MATURITY AND INCIDENCE OF OTITIS MEDIA

STATE OF DEVELOPMENT	MUNBER AUTOPSIED	CASES OF OTITIS MEDIA	PERCENT WITH OTITIS MEDIA
Immature (500-999 grams)	19	5	26.3%
Premature (1,000-2,499 grams)	45	23	51.1%
Mature (2,500 grams, or 50 cm crown-heel length)	37	28	75.5%
TOTAL	101	56	55.4%

MATURITY AND OTITIS MEDIA

Table XIII summarizes the relationship of the stage of development and the incidence of otitis media in this series.

There are several factors which must be considered in reviewing the almost straight line increase in percentage of otitis media with maturity. The more immature the infant, the shorter the time possible for developing otitis media. The more common causes of death, which vary with the stages of maturity, should be considered. In the four cases of birth trauma, one was immature, two premature and one of borderline maturity, 2,500 grams, 49 cm. The mechanisms leading to death in birth trauma are not usually associated with inflammatory reactions.

The syndrome of diarrhea, dehydration and electrolyte imbalance occurred in three mature infants only. Such entities help to explain the higher incidence of otitis media in mature infants. However, pulmonary hyaline membrane changes, a non-inflammatory lesion, which is highest in the premature group, revealed only one instance of otitis media in the absence of inflammatory lesions in other organs. This particular lesion helps to explain the lower incidence of otitis media in prematures than in mature infants; however, it does not aid in explaining the increase in otitis in prematures over that found in immature infants.

SUMMARY

The middle ears of 101 infants, including one stillborn, have been examined at autopsy for morphological changes of inflammation.

The findings have been correlated with inflammatory changes in other organs.

Each infant has been placed in a particular disease group.

The clinical history has been elucidated when deemed necessary.

The relative incidence of otitis media in immature, premature, and mature infants have been given for these 101 cases.

A few cases of otitis interna and otitis externa were found, and have been treated in the same manner as otitis media.

CONCLUSION

In general, otitis media is found in this series to correlate in a high percentage of cases with inflammatory changes in other organs and has been found usually, but not always, to be absent in deaths due to non-inflammatory lesions.

Otitis media, as demonstrated at necropsy, is least common in immature infants, more common in prematures and most common in mature infants. This correlates with the inflammatory changes, found at post mortem examination, in other organ systems in these three groups.

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XXXI

THE EFFECTS OF ANESTHETICS UPON THE EAR

III. TETRACAINE HYDROCHLORIDE

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PRINCETON, N. J.

In earlier papers^{7,8} it was pointed out that the use of topical anesthetics is considered by many surgeons to be a suitable method for anesthetizing structures of the ear during surgery. The favorable conditions accompanying the use of topical anesthesia have been discussed by Pitkin⁵ and Goodman and Gillman.³ Among the favorable conditions which they discuss, the fact that the action of topical anesthetics is reversible and is followed by complete recovery is especially critical. It is clear that any topical anesthetic which adversely affects the sensitive structures of the cochlea is totally unsuited for otological surgery. Whereas Goodman and Gillman³ specifically point out that the action of local anesthetic drugs is followed by complete recovery of nerve function with no evident structural damage to nerve fibers or adjacent cells, data obtained in this laboratory indicate that a number of topical anesthetics produce very serious disruptions of the normal functioning of the cochlea when these drugs are applied to middle ear structures. The major effect noted involves a reduction in the magnitude of the electrical response of the cochlea. These losses have very serious implications for hearing.

The manner in which the cochlea transduces acoustical energy so as to stimulate the auditory nerve has been a source of speculation for many years. However, many auditory theorists have come to believe that the electrical response of the cochlea directly triggers the auditory nerve.^{1,2,4,9,10} According to the electrical hypothesis of auditory nerve stimulation, any reduction in the magnitude of the cochlear response cannot help but have deleterious effects upon hearing. Experimental evidence is now available to show that the magnitude

From the Princeton Psychological Laboratory. This work was supported by a grant between the National Institutes of Health and Princeton University NIH B-2125, and by Higgins funds allotted to Princeton University. Permission is granted for reproduction and use by the United States Government.

of the auditory nerve discharge is directly related to the magnitude of the cochlear response.⁴

It is possible that local anesthetics do not cause structural damage to nerve fibers even though they apparently cause serious damage to the hair cells of the organ of Corti. It is clear that the choice of anesthesia for otological surgery is an important matter, and one which needs further study.

The purpose of the present experiment was to study the effects of tetracaine hydrochloride (Pontocaine,[®] 2 per cent) upon the electrical response of the cochlea of the cat. In addition, the present paper reviews and compares the effects of the topical anesthetics which have thus far been investigated in this laboratory.

PROCEDURE

Each animal was anesthetized with a solution of diallylbarbituric acid and ethyl carbamate injected intraperitoneally in a dosage of 1 cc per kilogram of body weight. After a surgical level of anesthesia had been reached, the tympanic bulla was approached laterally through an oval incision in the skin covering the parotid gland. Removal of this gland and resection of the sternocleidomastoid, digastric, and stylohyoid muscles exposed the bulla.

One hole (diameter 6 mm) was drilled in the lateral surface of the bulla. This hole accommodated the wire from the active electrode which terminated on a piece of platinum foil placed on the round window membrane. In addition, the hole was used to gain access to the round window for the application and removal of tetracaine hydrochloride.

A tonal stimulus of 1000 cps was generated by a General Radio Type 913-C beat-frequency oscillator whose output was connected to a Daven Type T-693 attenuator. The output from the attenuator fed into a power amplifier which drove a Western Electric 555 speaker. A hard rubber tube which terminated in a cannula tied into the external meatus led aerial sound from the speaker to the tympanic membrane. Cochlear potentials picked up from the round window membrane were amplified and measured with a General Radio Type 736-A wave analyzer operated as a selective voltmeter.

The intensity of the tonal stimulus was adjusted initially so as to give a cochlear response of 50 microvolts. After the stability of

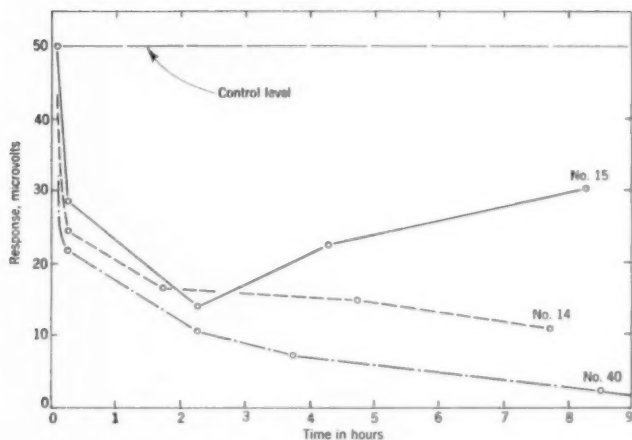


Fig. 1.—Losses in cochlear response through time for each of three animals following a fifteen minute period of application of tetracaine hydrochloride (2 per cent) to the round window membrane.

the response was assured, tetracaine hydrochloride (2 per cent) was applied to the round window membrane by means of a small nylon tube affixed to a hypodermic needle on a 1 cc syringe. The blunt end of the tube, placed in the bulla cavity through the drilled hole, was located directly over the round window membrane at a distance of about 2 mm. The dosage of tetracaine hydrochloride was always 0.25 cc. After fifteen minutes the anesthetic was removed by using the nylon tube as a catheter. In addition, the membrane was dried with a cotton wick. During the removal of the anesthetic, the active platinum electrode was removed from the round window membrane. A previous study⁶ shows that long term exposure of the middle ear cavity does not significantly change the cochlear potential.

The effects of tetracaine hydrochloride upon the cochlear response were evaluated in two ways. First, changes in the magnitude of the response produced by a constant stimulus were observed over extended periods of time. Second, intensity functions were plotted immediately before and after drug application, as well as at regular intervals following drug withdrawal.

All animals were isolated in an electrically shielded, soundproof room during the experiment.

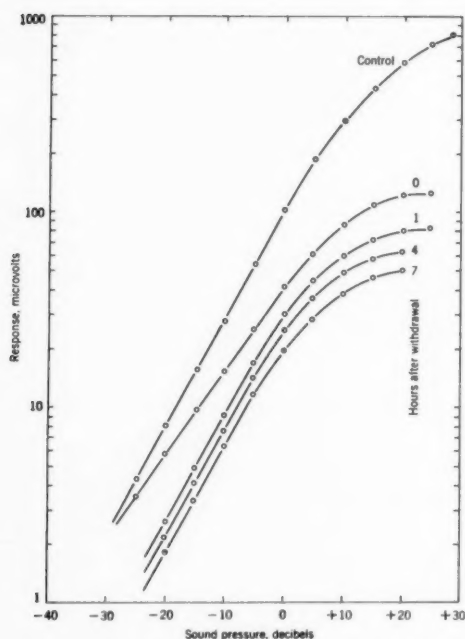


Fig. 2.—Intensity functions obtained on a representative preparation treated with tetracaine hydrochloride. This figure shows the cochlear output as a function of stimulus intensity before drug application (control), immediately following drug application (0 hours), and at several intervals thereafter. Intensity values given in decibels relative to 1 dyne/cm².

RESULTS

Application of tetracaine hydrochloride to the round window membrane resulted in an immediate and precipitous drop in the magnitude of the cochlear response. This drop may be ascribed to the electrical shunting effect of the solution. Figure 1 presents data obtained on each of three animals. Here may be seen the reduction in the magnitude of the cochlear response through time following a fifteen minute application of tetracaine hydrochloride (2 per cent) to the round window membrane. The shunting effect mentioned previously is not shown in Figure 1. During the fifteen minute period of application the response level typically fell to about five microvolts, and during this interval it was not possible to isolate the direct effect of the anesthetic from the shunting produced by the electrolytic

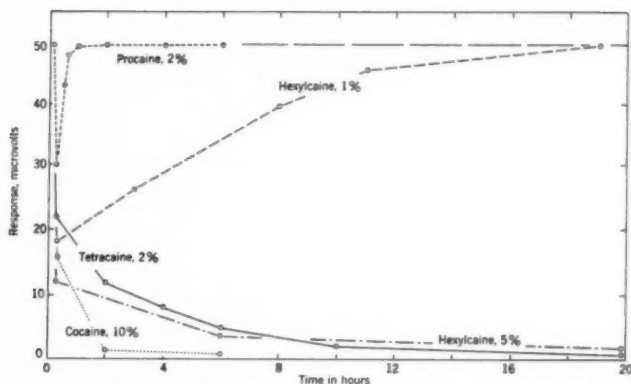


Fig. 3.—A comparison of cochlear response reduction for each of four anesthetic solutions applied to the round window membrane of cats for fifteen minutes. Each function is based upon data obtained from four or more animals.

action at the round window membrane. However, the direct effect of the drug became evident as soon as the round window membrane was dried, as may be seen in Figure 1. The loss in response immediately following drug withdrawal approximated 6 db in each preparation. Two hours after withdrawal the response had declined further to a level approximately 14 db below pre-drug level. Subsequent variations in response magnitudes differed slightly among the preparations, but in no instance was there a clear indication of full recovery. In one preparation (animal 40, Fig. 1) the course of the response was followed for a period of 25 hours. During this period the response continued to decline although the rate was negatively accelerated.

COMMENT

Intensity functions obtained on a representative preparation (animal 14) are shown in Figure 2. From this figure three things may be noted. First, there is a progressive loss in cochlear output over the range of intensities studied; that is, for any given intensity the output of the cochlea is reduced more and more as the interval following withdrawal increases. Second, the maximum output is also progressively reduced. Prior to drug administration a stimulus of 20 db (re: 1 dyne/cm²) produced a response of about 600 microvolts where-

as 7 hours following drug withdrawal the same stimulus gave a response of only 50 microvolts, a loss of 22 db. Third, the slope of the intensity function obtained immediately after withdrawal (0 hours, Fig. 2) is lower than the slopes of the other functions. The normal slope approximates 1.0, thereby demonstrating that the cochlear response in microvolts is a linear function of sound intensity. The change in slope suggests that following the administration of tetracaine hydrochloride the cochlear response is no longer a linear function of sound intensity: it is negatively accelerated. This fact suggests that the anesthetic alters the efficiency of the action of the hair cells. It is interesting to note that the normal slope is restored within a few hours even though the response is still declining. A possible explanation of the temporary alteration in slope and the progressive and persistent loss in response is as follows: The anesthetic temporarily alters the efficiency of the transduction mechanism of the cochlea while at the same time producing cellular injury. The injury is reflected in the over-all reduction of the response inasmuch as the cochlear potential is a composite function representing the sum output of all active hair cells. The process responsible for cellular injury appears to be prolonged and does not stop with the removal of the anesthetic from the round window. The interference with hair cell efficiency, however, is a temporary phenomenon.

For purposes of comparison, data obtained in two earlier studies^{7,8} are included with those from the present study in Figure 3. Each function in Figure 3 is based upon data obtained from four or more animals. The concentration of anesthetic solutions was determined primarily by concentrations normally used in ear surgery. From this figure it is apparent that procaine hydrochloride (2 per cent) and hexylcaine hydrochloride (1 per cent) are the only solutions which allow full recovery of the cochlear response. Hexylcaine hydrochloride (5 per cent), cocaine (10 per cent), and tetracaine hydrochloride (2 per cent) all produced extensive losses in the cochlear response, and no evidence was obtained to suggest that the response would recover from the effects of these solutions. It should be mentioned here that the losses obtained with these solutions were not brought about by a general decline in the physiological state of the preparations. Control data indicate that even under conditions wherein the drugged ear fails to respond, the contralateral ear responds normally.

It was suspected that the hydrogen-ion concentration of the various solutions might be an important factor in determining whether or not the effects of the drugs would be reversible. Accordingly, the

pH value was measured for each solution but no systematic differences in action were found to be correlated with pH.

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The Scientific Papers of the American Laryngological Association

XXXII

MAN-MADE AIR

PROBLEMS AND LIMITATIONS

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Seventy per cent of the earth's surface is water. Ninety-nine per cent of this nation's overseas traffic is moved on the 70,000 miles of sea lanes of the world. Included in this traffic are the sixty-six vital imports this country needs—for we require seventy-seven strategic raw materials and are self-sufficient in only eleven. Without these vital imports, we could have not jet aircraft, ballistic missiles, telephones or television sets. These few facts should suffice to demonstrate the importance of controlling the seas to a maritime nation.

The submarine is particularly well suited as an instrument for the control of the seas. Its principal tactical advantage is that it cannot be seen nor detected by electromagnetic devices while submerged. It is, therefore, in a position to exploit the two major maneuvers of warfare, stealth and surprise. When the submarine is surfaced, however, it loses these advantages. The more it can stay submerged the better it can perform its mission.

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Department of the Navy.

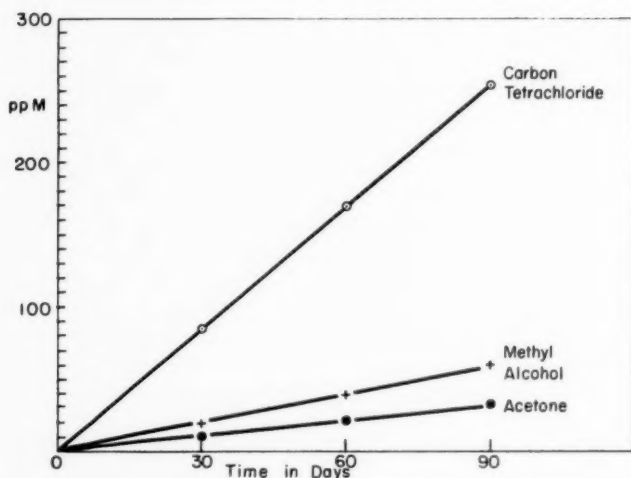
The opinions or assertions contained herein are those of the author and are not to be construed as official or reflecting the views of the Navy Department or of the Naval Service at large.

Prior to 1955 we did not have submarines in the true sense of the word. Those earlier submarines were really submersible torpedo boats. They spent the majority of their time on the surface and submerged only when necessary to launch an attack or escape from a pursuer. When running on the surface, the propulsive power was furnished by diesel engines. When submerged, this power was furnished by batteries. The submerged endurance was thus limited by the capacity of the storage batteries. Even at slow speeds, they would be exhausted in 36 to 48 hours. Therefore, it was necessary for the submarine to surface at frequent intervals to charge its batteries. The advent of the snorkel or breathing tube for submarines after World War II did not materially change this situation. The submarine was still attached to the surface, inhaling large volumes of fresh air, a necessity, since large quantities of oxygen are required for the combustion of fossil fuels. With nuclear power, our submarines now have an anerobic source of power and almost unlimited submerged endurance.

We now have a situation in which men are living in a completely sealed environment. One of man's first requirements is that he be provided with a respirable atmosphere. Our metabolism is aerobic, hence oxygen is required. In this same process carbon dioxide is produced. In our ordinary terrestrial existence, this carbon dioxide is utilized by the green plant life which in turn gives off oxygen. Such contaminants as are introduced by gasoline engines, drying paint, and cigarette smoking, are diluted in the vast atmosphere of the earth.

In the nuclear submarine, we have no such happy situation. In this closely confined atmosphere we must provide a breathing media which will preserve the health and efficiency of the submarine crew. In other words, we must *make* air. Man-made air has many problems in its production and will never be equivalent to the natural product.

Through the years we have learned that submarine crews consume about one cubic foot of oxygen per man per hour. In our submarines, we maintain the oxygen content of the atmosphere at approximately 21 per cent. This is done by adding oxygen to the submarine air as it is consumed. This can be accomplished in a number of ways; either by using oxygen stored in high pressure flasks; by chemical production of oxygen; or by the electrolysis of water. The carbon dioxide produced by the respiration of the crew must also be removed.



Accumulation of toxic substances in a closed environment. Vaporizing one quart in 100,000 cubic feet every 30 days.

Figure 1

One of the more serious problems involved in life in sealed environments is the continual contamination of the atmosphere by introducing small quantities of toxic materials. Figure 1 demonstrates this problem graphically. A hypothetical situation has been chosen in which one quart of a toxic substance is vaporized in 100,000 cubic feet every 30 days. One hundred thousand cubic feet is a very large space, e.g., a room 100 by 50 by 20 feet. Yet, if just a quart of carbontetrachloride is vaporized in the space over a 30-day period, the maximum allowable concentration of 90 parts per million has almost been reached. At the end of 60 days, the concentration would be in the neighborhood of 170 parts per million—and all of the occupants would be deceased. We solved this problem in submarines very easily, simply by not permitting carbontetrachloride to be taken on board. The accumulation of two other common solvents is also plotted. At the end of 90 days, the air would contain 60 parts per million of methyl alcohol, a level which would undoubtedly be damaging for continuous exposure. If a quart of acetone were vaporized

every 30 days, the concentration would reach 33 parts per million within 90 days.*

In substance then the principal problems in sealed environments are: a) providing oxygen, b) removing carbon dioxide, and c) preventing contamination of the air by other toxic substances. The temperature and humidity of the air must also be maintained within tolerable limits.

One may logically ask, "Where do these contaminants come from?" In general, they arise from three sources: first, those introduced in the construction and maintenance of the ship; second, those introduced by the crew and their activities; and third, those introduced in efforts to remove the first two. This last is not a facetious statement. The contaminants found in submarine atmospheres will now be listed and discussed. Following this my earlier statement will have more meaning.

CARBON DIOXIDE

This contaminant is produced by the respiration of the crew. Experience has shown that a respiratory quotient of one generally prevails. Therefore, about one cubic foot of carbon dioxide is produced by each occupant every hour. An intolerable situation would soon develop if this carbon dioxide were not removed from the air. Experiments conducted at the U. S. Naval Medical Research Laboratory during the period 1949 to 1954 disclosed that 1.5% was the upper limit of tolerance for carbon dioxide during prolonged exposures.¹ These findings were utilized in the design of equipment for continuous carbon dioxide removal. The device utilized for removing carbon dioxide on nuclear submarines is based on the principle that an amine solution sprayed in a scrubber tower will remove carbon dioxide from the flow of air passing up through to the tower. The amine combines with the carbon dioxide in a weak chemical bond and is collected as a solution at the bottom of the tower. It is then pumped to a heater where under increased temperature the carbon dioxide is released from

* The concentration of any solvent in the atmosphere in parts per million can be computed using the following formula:

$$\frac{\text{ml. of solvent vaporized} \times \text{Specific gravity}}{\text{Liters of air in space}} \times \frac{24.5}{\text{Mol. Wt.}^\dagger} \times 10^6$$

† Molecular weight of solvent

the amine, isolated, and then discharged overboard. The heated amine now cleared of its carbon dioxide is available after cooling for passage to the scrubber tower.² This chemical scrubber is not an unmixed blessing. The amine solution is volatile. Within limits, the greater the volatility of an amine the greater is its efficiency as a scrubbing agent. These amines as a class were known to be toxic, but there was no specific knowledge of the degree of toxicity for long-term exposure. It was necessary to determine the MAC for monoethylene amine and by scrupulous attention to the operation of the scrubber, to maintain its content within this limit in the submarine air.

CARBON MONOXIDE

During the early experiments on carbon dioxide, it was learned that carbon monoxide would be a problem in sealed environments if tobacco smoking was permitted. During "Operation Hideout" where 23 men were sealed in a submarine for six weeks, carbon monoxide concentrations in excess of 100 parts per million were encountered in the atmosphere.³ There is also considerable evidence that carbon monoxide is produced by the oxidation of paint.⁴ Since carbon monoxide is a rather insoluble and unreactive compound, there is only one way to remove it from the atmosphere, namely, to burn it. Therefore, burners have been installed on nuclear submarines through which the submarine air is passed over a heated catalyst. Here, the carbon monoxide is oxidized to carbon dioxide.

AEROSOLS

The tobacco smoking also introduces aerosols into the submarine atmosphere. Measurements indicate that with all air revitalization equipment operating, the aerosol content of submarine air will reach levels of 0.5 micrograms of particulates per liter or higher after a few days' submergence.² In order to maintain the aerosol content of the submarine air within acceptable limits, it was necessary to install electrostatic precipitators with high capacity. In general, an aerosol level of about .2 microgram per liter is considered desirable.

HEAT AND WATER VAPOR

It is convenient to consider these two contaminants together. They are produced by the metabolic processes of the crew, and the

steam power plant. The modern submarine also contains a large amount of electronic equipment which operates at a high temperature. This equipment adds a considerable heat burden to the submarine air. In order to maintain the temperature and humidity within acceptable levels, cooling coils are located at many points in the ship's ventilation system. These coils are cooled by expanding within them a common refrigerant, dichloro-difluoro methane or freon. Since the freon is compressed at a central location and delivered via piping at high pressure throughout the ship, leaks occur frequently. For all practical purposes, it is impossible to have a completely leak-proof system on any ship. A ship must be constructed in such a way that it will respond to a certain extent to the motions of the sea. A completely rigid ship would soon break up; therefore, every ship does what is known in maritime circles as "works." The working of the ship causes motions in the piping with accompanying minute leaks. Therefore, the submarine air is never without a certain amount of freon contamination.⁴ Freon in itself is not a particularly toxic substance. Industrial workers have tolerated concentrations as high as one thousand per million for 40-hour week exposures. The problem with freon is that it is readily decomposed by heat. Therefore, the freon is oxidized to form hydrogen chloride and hydrogen fluoride in the carbon monoxide burner. In order to overcome this problem, it is necessary to install an absorbent cylinder on the outlet side of the carbon monoxide burner.

HYDROCARBONS

A study of submarine air during the first prolonged submergence of the Nautilus revealed a significant content of aliphatic hydrocarbons with traces of aromatics. The principal source of these hydrocarbons is found to be a liquid solvent called "mineral spirits." This liquid solvent is used for cleaning and brightening of painted and metallic surfaces. Between 100 and 200 gallons of this material might be on board at any time. Several gallons of this material might be used daily in judicious cleaning of the ship. Under prolonged submergence, all this is volatilized to the submarine's atmosphere. Further investigation disclosed that most of the aromatic hydrocarbon was entering the submarine atmosphere by the volatilization of paint solvents. It was found that volatile hydrocarbons may continue to be released for as long as two or three weeks after it is applied. A third source of hydrocarbons indicated was the use of liquid deck wax

in submerged submarines. Ebersole² has presented data showing a two-fold increase in the hydrocarbon content of the air within one hour after deck wax was applied.

The foregoing discussion should provide a general view of the problems involved in providing a satisfactory atmosphere in sealed environments. It should be apparent that the contamination of a sealed environment atmosphere can only be avoided by one of two methods: either the introduction of the contaminant must be prevented or a system must be designed to remove it. If the introduction of a contaminant cannot be prevented, the following steps must be taken: 1) maximum allowable concentration for prolonged exposure must be established; 2) a system must be designed to remove sufficient amounts of the contaminant to keep it at this level; 3) an analytical method must be designed by which the level can be detected in the atmosphere.

At this point one might ask, "Why settle for a maximum allowable concentration; why not remove all of the contamination?" Atmospheric contaminants can only be removed by utilizing a chemical reaction—either oxidation or the formation of a compound. The efficiency of any chemical reaction is directly proportional to the concentration of the reacting substances. Therefore, the lower we desire to keep the concentration of any contaminant the larger by many times must be the reacting surface or absorption column and the more times per unit time the air must be passed over the reacting surface. This latter requires a great increase in the ventilation system required to move the air. It would be possible to design a submarine with an ideal atmospheric control system but there would be no room to carry weapons.

SUMMARY AND CONCLUSIONS

1. The successful operation of nuclear submarines creates a situation in which men must live for prolonged periods in a sealed environment.
2. The most immediate and pressing problem in a sealed environment is the necessity for providing a respirable atmosphere.
3. The three principal problems are: a) providing a replacement for oxygen utilized by the crew members; b) removing carbon dioxide

and other metabolics and c) a prevention or control of the introduction of other contaminants.

4. The principal limitation of man-made air is that all of the atmospheric contaminants can never be removed.

NAVY DEPT. BUREAU OF MEDICINE AND SURGERY

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XXXIII

MAN, DRUGS, AND SPACE FLIGHT

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There is probably no one adventure that has so captured the interest of the public mind in recent times as has the preparation for man's journey into space. As in any venture into an unknown or new frontier, there is great concern expressed over the various hazards which are known and even more about those which are unknown. Columbus must have had these same concerns and also had many well-meaning groups and individuals supplying ideas about how he could protect himself against these hazards. The rocketing of man into space has exposed him to more serious degrees of the same hazards which he has previously encountered in high performance aircraft flight. There will undoubtedly also be some new hazards to face. We are well aware of the fact that this environment will stress man beyond his physiological tolerances unless we do something to "make up the difference." Traditionally we have used either protective devices or equipment, or tried to alter man himself. In most such endeavors time is a factor and thus we cannot wait for evolution to change man. The use of drugs for this purpose is the next logical suggestion, and has been tried on many occasions. Today I would like to describe the problems engendered by the space environment, outline the profile of a space mission, and then discuss some suggestions that have been made for extending man's abilities on such missions.

We have mentioned the fact that most of the medical problems of space flight are extensions of those encountered in current jet aircraft flight. This is well-illustrated by the demarcation of certain physiologically space equivalent altitudes which are well within our atmosphere. Man suffers from physiological insufficiency even from 10 to 50,000 feet. The area extending from 50,000 feet to 120 miles is partially space equivalent for man, and above this the environment is totally space equivalent even though he may be some 480 miles from the border of true space as defined by the physicists.

As we ascend into the atmosphere, we find that the decrease in barometric pressure brings about a corresponding decrease in the partial pressure of oxygen, and the early symptoms of hypoxia may be manifested at altitudes as low as 5,000 feet in the form of diminished night visual acuity. This is augmented by headache and more rapid respiratory rate shortly after the 10,000 feet level is reached, and more serious difficulty above this altitude. Hypoxia is usually avoided by either pressurizing the aircraft cabin or providing oxygen equipment. Continued ascent to 50,000 feet would lower the atmospheric pressure to 87 mm Hg and would bring about anoxia, for all the pressure space in the lung alveoli would be occupied by carbon dioxide and water vapor. Time of useful consciousness for the unprotected man at this altitude is limited to the lung to brain circulation time (8-15 seconds). The use of partial and full pressure suits provides adequate protection against hypoxia and ultimate loss of consciousness.

The decreasing barometric pressure alone produces a symptom complex termed *dysbarism*.¹ These symptoms, which may occur in severe form at altitude as low as 25,000 feet, include the well-known group resulting from gas expansion in body cavities, and the less well-known group resulting from or initiated by evolved nitrogen. Many of you have probably experienced pain in the ears, sinuses, teeth, or intestinal tract either on ascent to altitude or more commonly, for the ears and sinuses, on return to sea level after flight to altitude. Nitrogen bubbles evolving from body tissues and fluids produce pain about the joints (bends), cough and substernal burning (chokes), various neurological phenomena such as visual field defects, paralysis, etc., a mottled skin rash, and even neurocirculatory collapse resulting in death. Numerous in-flight cases have recently been reported.² Denitrogenation prior to flight or adequate cabin pressure will afford protection.

At approximately 63,000 feet the barometric pressure has dropped to 47 mm Hg. If man's blood and tissue fluids were exposed to this altitude they would "boil," a condition called ebullism.

In the 70-120,000 foot area there is a concentration of ozone which is toxic for man. This substance may be concentrated by the compressors and levels of of 6 ppm for one hour may produce pulmonary edema.³

The most modern compressors are incapable of producing a pressure habitable atmosphere above an altitude of approximately 80,000 feet. Thus the sealed cabin rather than the pressurized cabin must be utilized above this altitude. The many environmental control problems of pressure, oxygen, carbon dioxide, water vapor, odors and wastes, temperature, etc., are thus introduced in addition to the problem of confinement.

Primary cosmic radiation becomes a hazard to consider at about 120,000 feet. These high energy particles (80% protons, 19% alpha particles, and 1% heavy nuclei) produce dense ionization tracts in tissue characterized by collision and thin down phenomena. Current information leads us to believe that astronauts in low orbits (less than 500 miles) should have no excessive radiation exposure problems. A great deal more information is needed about the Van Allen belts and radiation fields in space, however. The Van Allen belts form bands at the equator (1400-3400 miles, and 8,000-12,000 miles from the earth) capable of rendering dosage levels of 10-100 rads/hr.⁴

Ultraviolet rays also reach their unshielded potential at the 120,000 foot level and protection of the eyes is necessary.

The meteor hazard must be considered at 400,000 feet. It now appears that the chance of a large hit is unlikely, but erosion of optical and other surfaces is most likely.

The achievement of space flight requires exposure of the astronaut to accelerative force. Approximately 828 g seconds of exposure are required to attain orbital velocity and 1152 g seconds to reach escape velocity. Through the use of proper equipment and positioning, man is capable of withstanding the required exit and re-entry g loads.⁵

The loss of even the normal one g load of gravity resulting in weightlessness is an interesting phenomenon produced by the speeds of space flight. While the recent Russian and U. S. space flights should provide some needed information, unfortunately the majority of our studies have been for very brief periods in parabolic flight of fighter or transport type aircraft. Several of man's vital functions plus his performance of psychomotor tasks have been studied in these brief periods.^{6,7} We await an orbital laboratory for conclusive answers on

man's response to prolonged weightlessness and are particularly concerned about his ability to withstand accelerative forces after exposure to long periods of zero g.

Having outlined the various hazards lurking in the space environment, we will omit the details of selection of a bold adventurer to challenge this domain and now discuss a probable mission profile. A good example for our use is the proposed orbital mission for the Project Mercury astronauts. As you all know there is an extensive period of training, including the ballistic shot so successfully completed by Astronaut Shepard. Following this the man selected to fly the first mission will begin the Pre-Launch Phase lasting several days. This will include the ingestion of a low residue diet and numerous system checks as in the Redstone shot. A few hours prior to launch he will be dressed in his full pressure suit and after inevitable delays he will be strapped tightly to his form fitting couch in the capsule approximately two hours prior to launch. The entrance hatch will then be secured with 140 nuts, bolts, and screws. The capsule checkout procedure takes only about 30 minutes, so for approximately one hour he will have to sit secure in his capsule waiting for T minus zero or a sudden emergency abort signal which will send him 2500 feet into the air with an accelerative force lasting slightly over one second and peaking at about 20 g. If no emergency occurs and all goes well, the Atlas will accelerate to a peak of 8 g in a little over two minutes. Staging then occurs and the acceleration drops abruptly to one g but builds up to 9 g by sustainer burnout. The capsule and contents are then abruptly weightless. Approximately 5 seconds after sustainer separation the autopilot will stabilize the capsule, rotate it 180° in the yaw axis and also 35° base up in the pitch axis so that it is in the retrofire position. This is to assure that retrofiring can occur at the earliest possible moment to avoid landing on the continent of Africa if full orbital velocity or programmed orbit parameters have not been obtained. We have recorded no active role for the astronaut to this point, but he is playing a crucial passive role. He must monitor those instruments and indicator lights which indicate proper function of the rocket or which may indicate malfunction. His left hand will always be on the abort handle and he can fire the escape rockets at any time after the Atlas has ascended two inches off the launching platform. The pilot must be alert to note any errors of automatic function. If these occur he must activate the cabin oxygen purge bottles, escape tower jettison 15 seconds after staging,

capsule separation from the sustainer, and manually orient the capsule for retrofiring. After stabilization in orbit he must maneuver the capsule if he is to make purposeful observations of the earth and sky. The control device for doing this differs significantly from the usual aircraft control stick. Pitch is controlled by radial and ulnar deviation of the wrist; yaw by flexion and extension of the wrist; and roll by supination and pronation. Control is complicated by the lack of aerodynamic damping in space, and any movement initiated will continue until an equal and opposite force is applied. The recent flight demonstrated effective control in these axes.

Once in orbit, the pilot will be expected to make periodic and frequent reports to ground tracking stations. This vital information must be accurate. He will monitor cabin pressure, oxygen and carbon dioxide, and oxygen tank pressure. He will be called upon to make a variety of scientific observations. He will also navigate with the use of the earth viewing periscope. The faceplate to his suit must be manually closed in the event of a decompression, and the pilot must then be astute enough to analyze his situation and act. If at all possible he should not initiate re-entry at a point which would result in his landing anywhere but in the primary or secondary recovery areas. He must be prepared to survive any place between about 40 north and 40 south latitude.

Shortly prior to the completion of the third orbit, the capsule will be prepared for re-entry. It must be oriented with its broad base forward and elevated at an angle of 35° . If this is not done automatically, the astronaut must do it. This position must be attained prior to reaching the predetermined point where the retro-rockets are to be fired. If the capsule is out of alignment beyond specified limits, a locking device prohibits firing of the retrorockets. The exact center of gravity cannot be predicted and thus the vehicle attitude may be altered by thrust misalignment. The astronaut must correct this. After retrofiring, the capsule is oriented into the re-entry attitude which is a base down angle of 1.5° . As the aerodynamic forces build up on re-entry, oscillations occur in the attitude of the capsule. Though the reaction jets will not be able to stop these, proper application will keep them within acceptable limits. At 10,000 feet a ribbon parachute deploys and lowers the capsule to the surface with an impact of 30 feet/sec. The pilot may have to activate the chute. He

may then remain in the capsule and await pickup or get into a raft and do the same.⁸

Now that we have outlined the job of the early astronaut and the hazards he will face in the space environment, there is little wonder that there has been speculation on extending man's ability by various means, particularly when we consider prolonged missions. It should be emphasized that in using the Mercury mission for an example we do not mean to imply the use of drugs in this specific project; our discussion involves space flight in general. The demands of the space conquest are pushing at the tolerance limits in all the scientific fields, and the human and medical one is no exception. Though our margins of error are almost infinitesimal in the current high speed, high altitude aircraft, they have virtually disappeared in the space environment.

If we were to use drugs as a means of extending man's performance, where and how might this be done? The conceivable uses fall into three broad categories:

1. Treatment of some present loss or deficit.
i.e. anti-fever, meal pills, appetite reducers, norepinephrine.
2. Prophylaxis of some anticipated deficit.
i.e. antibiotics, antihistamines, radiation drugs, metabolism reducers (hibernation).
3. Enhance natural capability.
i.e. stimulants, hypnotics, tranquilizers, and mescaline.

Oberth as early as 1929 recommended the use of scopolamine for the treatment of space sickness. In more recent times there have been many suggestions which are less well-founded. One of the most recent of these suggested that "since space pilots would certainly develop hallucinations within days if not hours after take-off, they should be given hallucination drugs to block the incapacitating visions." This should "ignite a controlled mental fire to fight an uncontrolled mental fire." It was suggested that lysergic acid and mescaline might be tested in this regard. My previous comments on the job of the astronaut leave little doubt of the necessity of peak

performance and alertness. The use of any such drugs to produce dream states has no place in this performance. Numerous research studies have shown the possibility of development of hallucinations with rigidly channelized attention and severe reduction in sensory input. These may be prevented however by providing adequate sensory input, or simply keeping the pilot busy. This should be no problem on short missions, but the situation may be altered in interplanetary flights. The words of the proposer are judgment enough against this proposal, "We don't know the drug effects on the human psyche in space conditions," and we might add or even enough in earth conditions.

The use of the tranquilizers has also been suggested to allay anxiety prior to or during space flights. These drugs too produce a less than normal individual with unpredictable mental attitudes. They alter judgment and change orientation to reality. In addition it has been shown that the tranquilizers reduce the pilot's tolerance to stress of several types such as altitude, acceleration, etc.⁹ This would be a side effect which could not be accepted.

In prolonged space flight or even at the critical points of shorter flights, the use of stimulants has been suggested. The need for increased vigilance in a fatigued pilot at such critical times as re-entry or landing can hardly be questioned. Research has shown that the amphetamines are capable of mitigating fatigue and improving performance at psychomotor tasks. They appear to be useful in increasing and maintaining alertness. Missions and equipment should always be planned within the capabilities of the crew, then, if it is absolutely necessary to further extend performance, drugs such as the amphetamines may be used at crucial points if they are carefully controlled. Repetitive use should be avoided for it is not possible to make a superman with these drugs and it is possible to overextend man. In the future it may even be feasible to effect some control over diurnal or work rest cycles by the use of improved sedatives and stimulants. This must be investigated.

Some planners have looked into the future and the problems of interplanetary flight. The use of hypothermia to reduce metabolism and thus diminish the supplies of oxygen, food, etc., necessary on journeys of years has been suggested. Some basic studies are being done in this area, stemming from the use of hypothermia in surgery. The

development of a metabolism lowering drug to aid or supplant the hypothermia has been considered. At present small doses of meperidine, chlorpromazine, or promethazine are used to stop the shivering of patients undergoing hypothermia. It would seem that hypothermia for space pilots is still in the Buck Rogers status, for certainly no human in this state would do any performing of value.

Some fanciful writers have reported increases in the sexual drives of those going to space. Others have suggested that on prolonged missions or in missions with mixed crews some anti-sex drugs should be used. You may draw your own conclusions regarding these statements. It is quite possible, however, that the early women astronauts should be given hormonal therapy to stop menstrual flow until the mission is complete.

Considerable research effort will be necessary to determine which drugs will be useful in space flight. What should be investigated and what are the needs of the crewman for assistance by drugs? There are two basic principles which must pervade any decision to use drugs. First, any drug which is considered must have a thorough investigation into its specific modes of action not only in our normal environment, but at least in a space simulated one. Second, any drug selected for use must have a pre-test on each individual who is to use it. The testing of reactions to various drugs has even been suggested as a selection tool, predicated on the theory that drugs would be used in space flight and that such reactions would help to select among equally qualified candidates.

In the pre-flight or pre-launch period several drugs might be considered. There is little doubt that the astronaut will be quite excited and no doubt will have difficulty getting adequate rest prior to the flight. Hypnotics have been used prior to long missions to secure adequate rest, but performance decrement has been reported as long as 15 hours post ingestion. If necessary to obtain rest, some short acting hypnotic might be considered. In order to assure a calm astronaut the tranquilizers might be considered. These have been discussed previously, and their use is *not* recommended in our present state of knowledge. Consideration might be given to using antibiotics for prophylactic reasons. The value of such a procedure would have to be weighed against the risk of reaction. In such a costly enterprise as the first few flights, this might be good insurance in the carefully

pretested pilot. The hypotensive response to an intramuscular injection of mecholyl has been used as a selection test. It has been felt by some that this response is related to psychological status and thus to epinephrine-norepinephrine release and stress tolerance. Release of norepinephrine has been correlated with aggressive behavior, or the "tiger type." Perhaps in the future it may be possible to give an individual injections of a norepinephrine substance and make him a tiger. This may also be dangerous for it may place the drug-created tiger in a situation with which he cannot cope either psychologically or physiologically.

During the orbital phase of the mission the following might be considered. The weightless state may well create a form of motion sickness and thus anti-motion sickness drugs should be available. This may be particularly applicable if artificial gravity is supplied by rotating the space craft. In this event these drugs will alleviate labyrinthine effects of the Coriolis phenomenon produced by head movements during the rotation. On prolonged missions a drug to reduce the appetite, pills containing a meal, vitamins, and perhaps the analeptic drugs for critical periods would be useful. The possibility that the goals of hypothermia will be accomplished by pharmacologic means, as suggested in the work on artificial hibernation, should not entirely be disregarded. Chlorpromazine has been employed in a "lytic cocktail" to produce a state of general depression termed "artificial hibernation." Again, it is questionable whether such a hibernating pilot would be of value.

The radiation bands mentioned previously make it obvious that a drug protecting the pilot from an excessive dose of radiation would be valuable. The work in this area to date has not produced an acceptable drug. The energy sinks such as the sulfhydryl drugs (AET, glutathione) are toxic in helpful doses and give a variable response. They may provide 50% protection by reducing the effect of 1000 r to that of 500 r, but are no good for 700 r. The replacement bridges for the depleted hematopoietic system, such as autologous bone marrow, are palliative, and would be impractical in the space situation. The supportive drugs such as antibiotics, sedatives and tranquilizers would be for after the fact use. As of now no one drug will protect man.

In the re-entry and recovery phase the anti-motion sickness drugs and the analeptics might again be useful—the former particularly in

the rather severe oscillations of re-entry and the floating at sea awaiting recovery.

In conclusion then it would seem that a carefully selected and trained astronaut would better accomplish his mission without being under the influence of drugs. On prolonged missions he might be aided by the careful choice of drugs. We would prefer that he actually view Venus rather than hallucinate her through drug therapy. Prior to any drug use we must secure exact information on the specific mechanism of action, the toxicity, and the effect on performance of man in the space situation for each drug. The results of the clinical trial on ill patients and the determination of the LD/50 on rats is not enough information in this new environment where the margin of error is nonexistent.

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XXXIV

THE TREATMENT OF HEAD AND NECK CANCER WITH THE CONTINUOUS ARTERIAL INFUSION OF METHOTREXATE AND THE INTERMITTENT INTRAMUSCULAR ADMINISTRATION OF CITROVORUM FACTOR

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An increasing number of cancer chemotherapeutic agents have been developed and are currently in use in the management of incurable cancer in man. Definitive clinical studies have demonstrated that the usefulness of these compounds in the management of human cancer is largely limited to the leukemias and lymphomas.¹⁻⁴ Carcinomas of the head and neck region have shown only a slight and variable response to these compounds.^{1,4-6}

The different classes of chemotherapeutic compounds that have received some clinical trials in head and neck cancer include the alkylating agents (e.g., Nitrogen Mustard, Myleran, Cytosan, etc.),^{3,7-11} antimetabolites^{5,6,12} (purine analogues, pyrimidine analogues, antifolic acid compounds), antibiotics^{13,14} (e.g., Actinomycin D, Strepto-

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nigrin, etc.) and miscellaneous compounds^{15,16} (e.g., Mitomycin C). Clinical reports have indicated that the systemic administration of these chemotherapeutic agents has resulted in little practical value in the management of most head and neck neoplasms.

Greater interest in the cancer chemotherapy of these neoplasms has centered around the regional administration of chemotherapeutic compounds in an attempt to enhance the anti-tumor effects in a given area. It has been shown that the arterial administration of Nitrogen Mustard (HN2) will produce profound local effects on normal structures as well as regressive effects on a variety of tumors that have not been observed after the intravenous use of this drug. Thus, the intra-arterial administration of HN2 into the external carotid artery has resulted in objective tumor regression of a variety of neoplasms as well as severe radiomimetic effects on normal structures in the distribution of the artery injected.^{17,18} However, the practical usefulness of this form of therapy is sharply limited by the lack of specificity of HN2.^{19,20}

It seemed feasible to extend the clinical studies of the arterial route of administration of chemotherapeutic agents in head and neck cancer to compounds having a more specific antitumor and antimetabolic effect^{1,12,21-24} than have the alkylating agents. Over the past several years, a number of antimetabolites have been studied by this route of administration, including the glutamine antagonists O-diazoacetyl-L-Serine (Aza serine), and 6-diazo-5-oxo-L-Norleucine (DON); the pyrimidine antagonists, 5-Fluorouracil, and 5-Fluoro-2'-deoxyuridine, and the anti-folic compound 4-amino-N¹⁰-methyl pteroylglutamic acid (Methotrexate).²⁵ Antimetabolites, however, require a more prolonged period of action before clinical antitumor effects are produced.^{26,27} It seemed reasonable, therefore, to prolong the duration of administration of an antimetabolite in order that those cells which at any given moment are in a metabolically inactive phase, might be affected by the antimetabolite as they sequentially enter a metabolically active phase.

The biologic effect of many antimetabolites can be effectively prevented by the concomitant administration of the specific metabolite (antidote).^{4,28,29} It was postulated that the continuous arterial (regional) administration of supralethal doses of an antimetabolite, together with the intermittent use of the metabolite (antidote) sys-

temically (i.e., intramuscular) might result in an enhanced differential anti-metabolic effect in the regional area, while the vulnerable systemic areas of the body (i.e., bone marrow) were protected by the antidote.

A method of therapy has been developed embodying these hypotheses as follows: The continuous 24-hour administration of an antimetabolite through a catheter inserted into a known site in the arterial blood supply of localized forms of head and neck cancer, together with the intermittent, intramuscular administration of the specific antidote. Clinical studies using Methotrexate as the antimetabolite and Citrovorum Factor (Leucovorin, C.F.) as the metabolite (antidote) have been described in patients with incurable head and neck cancer and other relatively localized neoplasms.³⁰⁻³⁴ This method of therapy is to be distinguished from extra-corporeal isolated perfusion³⁵ which embodies the temporary exclusion of the tumor bearing area from the general circulation for periods of 30 to 60 minutes during which time high concentrations of a drug are perfused in the isolated part.

The purpose of this communication is to describe further experiences with this method of therapy in incurable head and neck cancer.

METHODS

Selection of Patients. Patients with incurable, localized forms of head and neck cancer were selected for study. Patients with various types of incurable head and neck cancer without known metastases are the most suitable candidates for study. In some instances, a patient with an inoperable primary form of head and neck cancer, but with unilateral or bilateral resectable nodes may be a candidate for combination surgery and arterial infusion chemotherapy. In this situation, the neck metastases may be controlled with radical neck dissection while the inoperable primary lesion may be treated by arterial chemotherapy. Patients with various forms of primary head and neck cancer with diffuse bilateral neck metastases outside the distribution of the arteries catheterized (e.g., external carotids) and whose disease in these latter areas cannot be controlled, are not suitable candidates for this form of regional chemotherapy. Patients who have had prior radiotherapy whose recurrent or unresponsive disease is within the distribution of one or more of the external carotid

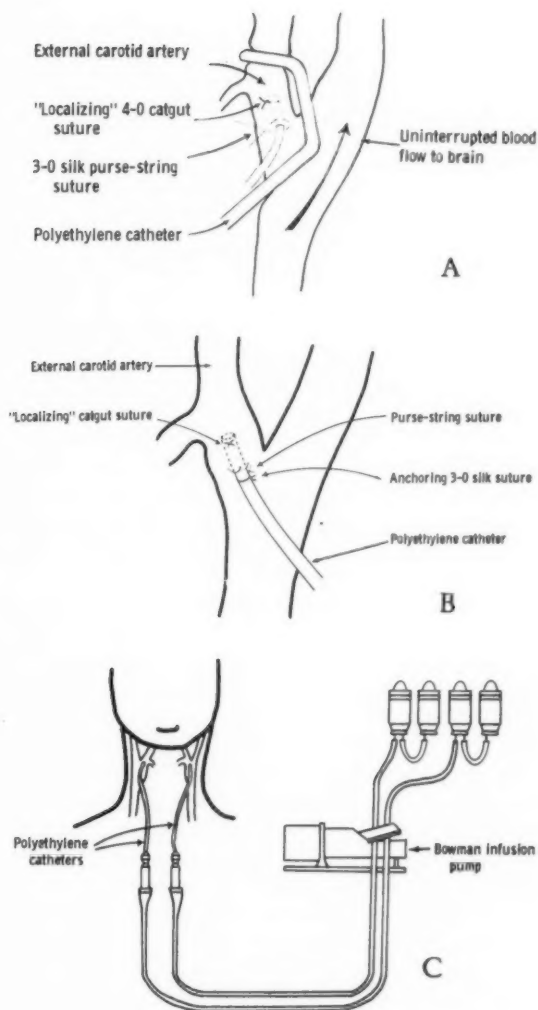


Fig. 1.—Catheter insertion and infusion assembly.

arteries are suitable candidates for a trial of the method of therapy herein reported.

Catheter Insertion. The catheter is prepared from PE-60 Clay Adams polyethylene tubing 18 inches long with an inside diameter of .030 inch and an outside diameter of .048 inch. The techniques of catheter insertion and infusion assembly have been described in detail elsewhere.³⁶ Briefly, the technique of catheter insertion is as follows: After adequate exposure of the distal 1 inch of the common carotid artery, the proximal parts of the internal carotid and the external carotid arteries has been obtained, and these vessels accurately identified, a No. 4-0 silk purse-string suture is applied to the distal part of the common carotid artery. Hemostasis is obtained with a Beck-Type arterial clamp, an incision is made in the center of the purse-string, and the catheter is inserted by means of a No. 4-0 catgut suture applied to the end of the catheter as shown in Figure 1A. The purse-string suture is tied as the hemostatic clamp is removed. In order to prevent subsequent displacement of the catheter, a No. 3-0 silk suture is applied to the catheter as it issues from the vessel, sufficiently tightly to "bite into" the catheter wall, but not tight enough to occlude the lumen. A free end of this suture is passed through the adjacent arterial wall and loosely tied (Fig. 1B).

The exact area to be infused is determined in the operating room and before the wound is closed by a fluorescein dye technique. Three to 6 cc of Fluorescite® are injected into the catheter slowly, the injection taking about 1 minute. An ultra-violet light will delineate accurately the area to be infused. Fluorescence will persist up to 30 to 60 minutes. In the external carotid area, fluorescence will be seen through the distribution of this vessel to the midline, including the skin of the upper neck, face, scalp, the tongue, palate, oral and nasal mucosa, hypopharynx, etc. A variable amount of absence of fluorescence is noted in the palpebrae and forehead areas, as these areas are supplied by the terminal branches of the internal carotid arteries. If the catheter has been inadvertently inserted into the internal carotid artery, only the latter areas will fluoresce.

In patients with bilateral head and neck cancer, catheters are inserted into both external carotid arteries through bilateral neck incisions. The catheter is brought out through the inferior margin of the skin incision, without fixation to the skin, flushed with saline and

the proximal end is clamped. The clamp is affixed to the anterior chest wall with adhesive tape, leaving sufficient slack to permit movement of the head.

Catheter Assembly. The infusion assembly is put in operation as soon as the patient has recovered and glucose and water or saline solution is infused to keep the catheter patent; therapy may be instituted at any suitable interval depending on the patient's general condition. A No. 20-gauge intravenous type needle is inserted into the free end of the catheter and the former attached to rubber tubing which passes through the fingers of a Bowman Infusion Pump and is connected through a drip chamber to liter bottles of infusate (Fig. 1C).

Dosage Schedules. An adequate course of therapy is defined as that amount of therapy that results in moderate local toxicity (diffuse unilateral or bilateral superficial oral ulcerations if unilateral or bilateral therapy) or systemic toxicity (mucosal lesions, hematologic depression).

The usual dose schedule used for unilateral catheterization was Methotrexate 50 mg/24 hours, infused in 1000-2000 cc of saline or glucose in water. The dose schedule for bilateral catheterizations was, Methotrexate 25 mg/side/24 hours, infused in 1000 cc of glucose and water or saline solution per side. Multiple liter bottles were set up in tandem to obviate the possibility of air embolism resulting from the inadvertent emptying of a single infusion bottle. The metabolite (antidote), C.F., was given in the dose of 6 mg every 6 hours intramuscularly. On these dose schedules, an adequate course of therapy as previously described required 5 to 10 days of continuous arterial infusion. At this time, the patient was rested and the catheter kept patent with the continuous infusion of glucose and water or saline solution. Further courses of therapy were given until maximal clinical benefit was obtained. This was noted in most cases after 1 to 3 courses of therapy had been given. It is important to follow the hemogram closely, especially the white blood count, to prevent serious systemic toxicity from the huge doses of Methotrexate given. After the third day the white blood count is obtained every 12 hours, and when definite leukopenia is evident, therapy is stopped or the amount of antidote (C.F.) increased. Patients with renal insufficiency do not excrete Methotrexate in a normal manner and severe toxicity may

TABLE I

RESULTS OF CONTINUOUS ARTERIAL INFUSION OF METHOTREXATE
AND INTERMITTENT INTRAMUSCULAR ADMINISTRATION OF
CITROVORUM FACTOR IN HEAD AND NECK CANCER

	NO. OF PATIENTS	NO. OF ADEQUATE COURSES*	NO. EVALUATED FOR THERAPEUTIC EFFECT	TUMOR RESPONSE	
				PARTIAL	COMPLETE
Epidermoid					
Carcinoma	40	31	27	21	6
Lymphosarcoma	6	6	6	4	2
Miscellaneous forms of cancer	2	2	2	1	0
Total	48	39	35	26	8

* See text for definition of "adequate course of therapy."

rapidly develop; considerably larger doses of the antidote are necessary in these instances.

RESULTS

Forty-eight patients with various types of inoperable head and neck cancer have had unilateral or bilateral external carotid catheterizations as follows: Epidermoid carcinoma, 40 patients; lymphosarcoma, 6 patients; miscellaneous forms of cancer, 2 patients (Table I).

There were 39 patients in whom at least one adequate course of therapy was given. An adequate course of therapy has been defined above and was considered to have been given when moderate local or systemic toxicity was noted. Four patients who received one adequate course of therapy were not evaluated for therapeutic effect because of the difficulty in determining the clinical extent of the disease. Thirty-five patients were evaluated for therapeutic effect. In 26 patients there was some partial objective tumor regression, often associated with clinical benefit. In the majority of these patients, cancer was present in contiguous areas outside the actual area of

infusion therapy. In 8 patients whose disease was confined to the area of therapy, there was total objective tumor regression.

In those patients in whom measurable disease was present in the areas of therapeutic infusion, response was noted as early as the 4th day and was characterized by a progressive decrease in visible tumor. The tumors appeared cleaner as they regressed and were apparently absorbed as the neoplastic cells were sequentially killed. Mucosa covered the sites of absorbed tumor, but in many cases, large defects remained, especially in patients with sinus tumors with extensive involvement of the hard palate; in these patients there were residual oro-nasal defects.

REPORT OF CASES

CASE 1. Epidermoid carcinoma of the maxillary sinus. The patient is a 72 year old white male whose diagnosis was established by biopsy in January 1959. There was diffuse involvement of the right maxillary sinus with extension to the naris and hard palate bilaterally. Bilateral catheters were inserted into the external carotid arteries in February 1959, and the patient received continuous arterial infusion of Methotrexate with intermittent intramuscular C.F. therapy over a period of six days. Total gross tumor regression occurred and the patient was free of apparent disease for eight months. Recurrence in the right maxillary sinus and soft tissues of the face occurred in September 1959 (Fig. 2A). Bilateral external carotid catheters were again inserted and the patient received a 15-day course of therapy in the following dosage: Methotrexate 25 mg/side/day; C.F. 6 mg intramuscularly every 6 hours. Progressive tumor regression occurred and by the 15th day there was no gross evidence of cancer (Fig. 2B). There were no manifestations of systemic toxicity due to Methotrexate. The patient was in remission for the next 15 months when a small lesion was noted in the right naris. On biopsy, this proved to be epidermoid carcinoma. This has responded to a third course of therapy and the patient is at present free of apparent disease.

Comment. Total gross tumor regression was noted in each instance following three courses of therapy given over a 22-month period. There was no apparent development of "drug resistance."



Fig. 2.—Case 1. Epidermoid carcinoma of the maxillary sinus. *Left*, before therapy. Note tumor extending into the soft tissues of the face. *Right*, after therapy. Note the total gross tumor regression that has occurred.

The patient is at present free of gross disease 28 months after the first course of therapy.

CASE 2. Epidermoid carcinoma of the hypopharynx. The patient is a 53 year old white male in whom the diagnosis of epidermoid carcinoma of the hypopharynx was established by biopsy in December 1960. He had had symptoms of increasing dysphagia, dysarthria and dyspnea over a 3 month period. There was a bulky, fungating tumor of the hypopharynx occupying the entire area of the hypopharyngeal wall posteriorly and extending to the lateral walls (Fig. 3). The mass was in contact with the epiglottis and limited the airway. There were no palpable neck nodes. On December 9, 1960, bilateral external carotid catheters were inserted and the patient received a 6-day course of infusion therapy as follows: Methotrexate 25 mg/side/24 hours; C.F. 6 mg every six hours intramuscularly. Progressive decrease in visible tumor occurred and the patient

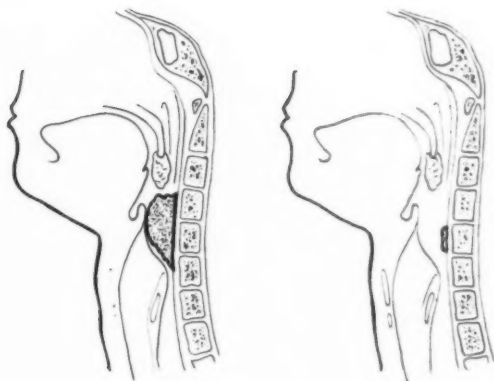


Fig. 3.—Case 2. Epidermoid carcinoma of the hypopharynx. *Left*, before therapy. Note the large, fungating tumor involving the posterior wall of the hypopharynx. *Right*, after therapy. Note the tumor regression that has occurred. There was a residual lesion on the posterior hypopharyngeal wall measuring approximately one cm in diameter.

became asymptomatic. A second five-day course of therapy was administered through the left external carotid catheter as follows: Methotrexate 50 mg/24 hours; C.F. 6 mg every six hours intramuscularly. On January 24, 1961, laryngoscopy demonstrated a slightly elevated lesion 1 cm in diameter on the posterior wall (Fig. 3B). Biopsy revealed epidermoid carcinoma. On February 10, 1961, excision of this area through a lateral pharyngotomy was performed. A skin graft was used to repair the posterior pharyngeal wall. The patient has remained free of gross disease to date, six months after onset of therapy.

Comment. This patient demonstrates the combined use of surgery and chemotherapy. An extensive fungating lesion of the hypopharynx was reduced in size by 90 to 95% by arterial infusion chemotherapy and was rendered easily resectable.

In those patients in whom partial tumor regression occurred, response has lasted for 1 to 3 months. In those patients in whom total

TABLE II
COMPLICATIONS OF CATHETER INSERTION AND INFUSION ASSEMBLY

	NO. OF PATIENTS CATHETERIZED	INACCURATE CATHETER PLACEMENT OR PREMATURE DISPLACEMENT	INFECTION AND BLEEDING	LEAKAGE
Epidermoid Carcinoma	40	6	8	3
Lymphosarcoma	6	-	-	2
Miscellaneous forms of cancer	2	-	-	1
Total	48	6	8	6

tumor regression occurred, response has persisted for periods of follow-up of up to 15 months, before relapse was noted.

Complications relating to catheter insertion, and maintenance of infusion assembly are tabulated in Table II. Varying degrees of local or systemic Methotrexate toxicity were noted in most patients. The former was characterized by a mucositis and slight erythema of the skin within the areas of therapy. Systemic toxicity was characterized by varying degrees of hematologic depression and non-specific, diffuse oral ulceration. In most cases, systemic toxicity was moderate and could often be controlled by adjusting the dose of the antidote.

COMMENT

The results of this study demonstrate that the anti-tumor activity of an antimetabolite (Methotrexate) can be increased in patients with head and neck cancer by regional administration (arterial infusion) in supralethal doses, when the specific antidote (C.F.) is given in appropriate dosage by the systemic route to protect vulnerable areas of the body (i.e., bone marrow, gastrointestinal tract).

The increased anti-tumor activity of Methotrexate noted in this study is considered to be related to the following factors: a) route of

administration - The arterial route of administration results in a higher local concentration,³⁷ and hence a greater local antimetabolic and anti-tumor effect; b) the systemic use of the antidote (i.e., intramuscular) permits the administration of supralethal doses of the antimetabolite as it reduces systemic toxicity, yet preserves some regional anti-tumor effect; c) the *continuous* 24-hour administration of the antimetabolite results in a *continuous* anti-metabolic effect, and hence, those cells that at any given moment are metabolically inactive may be affected as they sequentially enter an active metabolic phase.^{38,39}

The complications of catheter insertion and maintenance of infusion assembly were frequent and often serious (Table II). In six patients, there was inaccurate catheter placement or premature displacement. In eight patients, infection associated with varying degrees of bleeding occurred. In several patients, the hemorrhage was of such severity that ligation of one or more of the great vessels of the neck was necessitated. Leakage of infusate of varying degree was noted in six patients. In most of these patients, the leakage prevented the completion of therapy.

Inaccurate placement of the catheter may be prevented by careful attention to techniques of catheter insertion and the use of the fluorescein dye technique to accurately demonstrate the area of infusion therapy. Premature displacement of the catheter results from the inadequate application of the "holding sutures" as the catheter issues from the artery. Infection around the catheter, in most cases the cause of hemorrhage, is usually due to failure to observe rigid sterile precautions. It must be emphasized that the most meticulous sterile techniques must be used whenever the catheter or the infusion assembly is manipulated in order to obviate the serious complication of infection and hemorrhage.

Other methods of catheter insertion, including retrograde catheter introduction and the ligation of various arteries to develop collateral circulation into inaccessible areas are being explored to extend the usefulness of this method of therapy and to reduce the complications of techniques currently in use. Other dose schedules of Methotrexate and C.F. as well as other cancer chemotherapeutic agents are being investigated by this method of administration.

This method of therapy is in the area of clinical investigation and its possible place in the conventional therapy of head and neck cancer is not as yet clearly defined.

The casual use of this technique of drug administration is strongly discouraged; a team consisting of surgeons and cancer chemotherapists, cognizant of the problems of techniques and drug toxicity, together with a carefully planned program of clinical investigation is mandatory before initiating a program of regional infusion.

SUMMARY

The systemic administration of cancer chemotherapeutic compounds in patients with incurable head and neck cancer has resulted in little benefit in the practical management of these diseases.

A method of therapy is described which embodies the *regional* (arterial) 24-hour administration of supralethal doses of an anti-metabolite (Methotrexate), together with the intermittent use of the specific meabolite (antidote - Citrovorum Factor) to prevent serious systemic toxicity.

Techniques of catheter insertion and fixation, maintenance of infusion assembly and dose schedules are reported.

Forty-eight patients with various types of incurable head and neck cancer had unilateral or bilateral external carotid catheterization. There were 39 patients in whom at least one adequate course of therapy was given. Thirty-five patients were evaluated for therapeutic effect. Of these, 26 patients had partial tumor regression. In these patients, tumor was also present in contiguous areas outside the area of infusion therapy. In eight patients in whom tumor was present only in the area of therapy, there was complete apparent tumor regression. Response persisted from 1 to 3 months in the former category and up to 15 months in the latter category.

Complications were frequent and consisted of inaccurate placement of catheter or premature displacement of catheter - six patients; infection and/or bleeding around catheter - eight patients; leakage of infusion around catheter - six patients.

Techniques are being explored to extend this method of therapy to other areas of the body, and other chemotherapeutic compounds are being investigated for possible enhanced anti-tumor effects resulting from regional administration.

This method of administration is in the area of investigation and its place in clinical medicine is not yet defined. The casual use of this technique is strongly discouraged; a team consisting of surgeons and cancer chemotherapists, cognizant of the problems relating to techniques and drug toxicity, is mandatory before initiating a program of regional infusion.

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THE PROBLEM OF STOMA CONSTRUCTION
IN LARYNGECTOMY CASES

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The construction and management of an adequate stoma in laryngectomy cases has been a problem to us. The subject is presented here, not because we have very unusual ideas about it, but rather to stimulate discussion and ascertain how others deal with this situation. This is very little on the question to be found in the literature and relatively few textbooks give only meager space to a problem that, in our experience, is an important one. The tracheostomata in laryngectomy patients have an unbelievable tendency to close. The opening becomes inadequate and the patient is unhappy, uncomfortable and panicky. A secondary plastic operation is necessary in order to improve the airway, or a laryngectomy tube must be worn constantly.

There was some difficulty in the pre-antibiotic days when fistulae, accompanied by, or produced by infection, seemed to be factors that caused stomata to become small. When antibiotics became available fistulae and infections were much more infrequent and the problem of an adequate stoma was reduced to a minimum. But then it became known that practically all carcinomas of the larynx, except those situated on the vocal cords, readily metastasized to the nodes of the neck. We, therefore, began doing radical neck dissections in continuity with laryngectomies, whether nodes were palpable or not. This added more trauma to the operated field with increased scarring, causing narrowing and distortion of the stoma. Then, to augment this dilemma, virulent staphylococcus infections appeared in the best and most meticulous of our hospitals. Pharyngeal fistulae were again obtained in great numbers and the tracheostomata became small again. This was our experience and I have reason to believe, after

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verbally canvassing a few of our colleagues, that we were not alone in this distressing circumstance.

Let us review some of the reasons why a stoma has a tendency to close. The trachea may be small and its circumference is initially not adequate enough to allow for the scarring and shrinking that occurs with healing. The cartilages of the trachea may be rather thin and soft and unable to withstand the pressure of the surrounding scar contracture. Fistula formation with accompanying infection, or infection alone, will increase the cicatrization around the stoma. Infection of the edges of the opening, as well as perichondritis and chondritis of the tracheal cartilages, will reduce the size of the stoma. In some cases this may be due to the fact that the trachea has been freed too generously from the surrounding tissue, leaving an inadequate blood supply. The skin may not have been meticulously sutured to the mucosa of the trachea, permitting added scar formation. The stoma may retract into the suprasternal notch and prominent clavicular insertions of the sterno-cleido-mastoid muscles may approach the midline, making the retraction even more evident. Displaced, enlarged lobes of the thyroid gland may press upon the upper portion of the trachea, helping to narrow this area.

The addition of almost routine neck dissection to a laryngectomy has further influenced the situation with contracture of the tissue on the operated side of the neck. This is markedly increased when a fistula or an infection occurs. The stoma not only contracts but it is situated on a slant in the suprasternal area. This helps to narrow the opening and also may angulate the trachea just below the stoma.

To counteract this tendency for the tracheostoma to become reduced to a size that is inadequate, several procedures have been advocated. A "tongue" of mucous membrane is separated from the posterior portion of the cricoid cartilage and remains attached to the upper end of the stoma. The added mucosa can be carefully sutured to the skin and is more likely to heal by primary union. Of course, this cannot be done in a case of subglottic involvement. Also, the anterior surfaces of the upper two rings of the trachea are removed, leaving an oval opening which is larger than the circumference of the trachea. These maneuvers certainly help to obtain a larger opening, but are not always eventually successful because of the factors already mentioned that influence their narrowing.

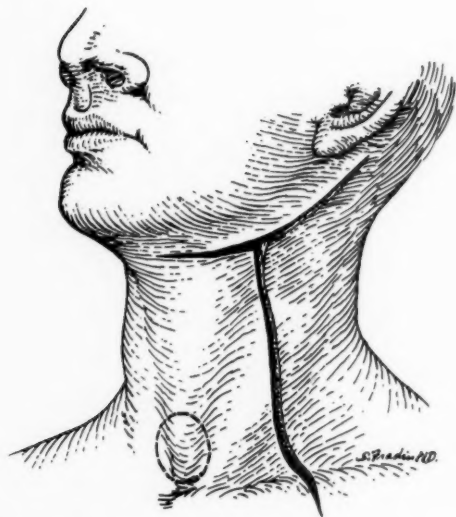


Fig. 1.—Area of excision of skin and subcutaneous tissue.

Another procedure which is sometimes helpful, is to preserve the lower portion of the cricoid cartilage. This leaves a firm cartilaginous ring at the mouth of the opening which would discourage contracture. However, at times this cartilage in its exposed position becomes infected and the stoma again becomes inadequate. On many occasions we have had to excise portions of the cricoid cartilage because of infection. Then, too, in using the cricoid cartilage, an involved pre-laryngeal node may be left behind.

Meticulous attention to the apposition of the skin of the neck to the mucous membrane of the trachea has always been advocated. Frequently this is not possible since the mucous membrane is within the trachea and it is difficult to draw the skin close to it and place sutures that will hold. It becomes necessary to use deep sutures that penetrate or surround the tracheal cartilages in order to obtain adequate apposition of skin to mucous membrane. These deep sutures may cause pressure necrosis and infection of the cartilages with subsequent narrowing of the opening.

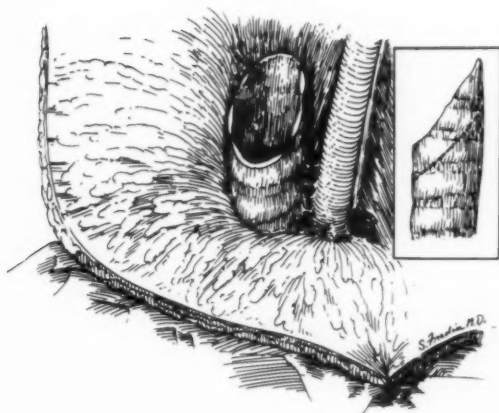


Fig. 2.—"Tongue" of mucosa and excision of anterior portion of tracheal cartilages. Insert—dotted line shows area of submucosal resection of additional tracheal cartilage.

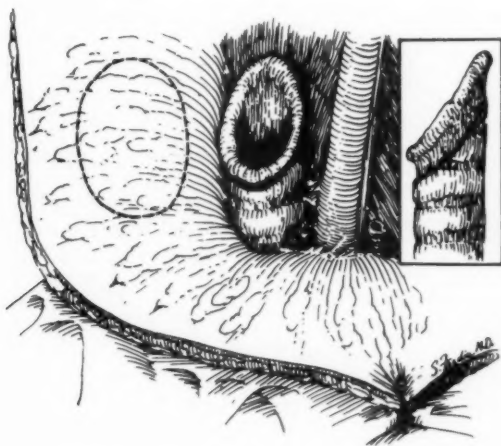


Fig. 3.—Submucosal resection of tracheal cartilage has been performed and mucosa is free and ready for suturing. Dotted line shows area of excision of skin and subcutaneous tissue.

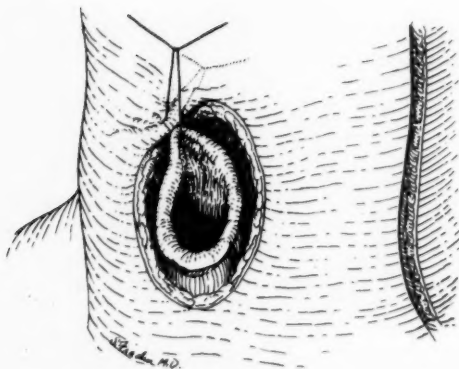


Fig. 4.—Beginning of suturing of mucosa to skin.

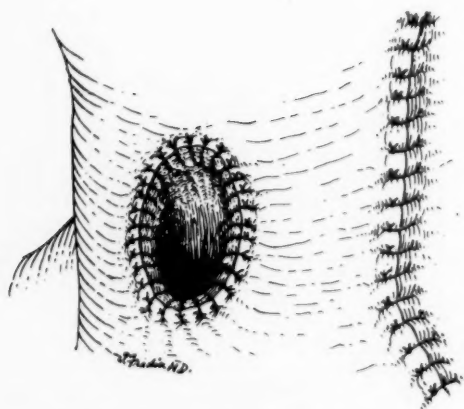


Fig. 5.—Final appearance of tracheostoma.

Of course, when the stoma becomes too narrow a laryngectomy tube can be worn permanently. At times we are able to recommend that the tube be removed during the day and replaced at night, but our patients do not wish to be harassed with the care of a tube, nor do they like to be seen with one. After all, their ailment is all too obvious to the people with whom they come in contact without the additional attention that a laryngectomy tube attracts. Then, too, the presence of such a tube frequently produces pressure upon the cartilage, mucous membrane and the skin of the stoma causing infection and perichondritis with further contracture.

We have used all the methods advocated, alone and in combination, with variable success. This, however, was not satisfactory, and with our past experience to draw upon, we modified these procedures to some extent. We have found that two maneuvers are important: A wide excision of the skin and submucosal excision of the tracheal cartilages around the stoma. The mucosal "tongue" from the posterior wall of the cricoid cartilage is used whenever possible. The anterior portion of the first and second rings of the trachea are excised so as to give an oval shape to the stoma. However, the amount of skin and subcutaneous tissue excised in this area is far greater than was previously removed. This helps to prevent some of the contracture by exerting a radial tension in all directions around and away from the stoma. We also attempt to compensate for the pull that the scarring of a neck dissection produces by making the skin excision a little toward the unoperated side. In addition, the remaining tracheal cartilage around the stoma for about the width of one or two tracheal rings, is removed by submucous resection with a scalpel or with a Freer elevator. The remaining tracheal mucosa can now be readily and carefully sutured to the skin edge without tension and without the use of deep sutures.

To advocate this procedure and say that it always produces the desired result is far from the truth. However, our results have improved, although we still have the factors of infection and fistulae to deal with. This, too, we have overcome to some extent. Previously, in closing the pharyngeal opening we used continuous chromic catgut sutures. This layer was reinforced with a secondary line of interrupted chromic catgut sutures, utilizing any available muscle and areolar tissue. We now use interrupted silk sutures in closing the

primary and the secondary layers. We feel that in this way a better, stronger and more meticulous closure of the pharynx is obtained.

In addition, we have given up the use of a feeding tube. We have long since felt that this tube was a source of irritation to the pharyngeal suture line and was so uncomfortable to the patient that he was forced to swallow frequently. This foreign body in the pharynx, rubbing against the sutured area, we feel, was the cause of many of the fistulae we obtained. We now feed the patient intravenously for five to seven days and encourage him to refrain from swallowing his saliva. At the end of that time the patient is given sterile water to drink, and his fluids by mouth are gradually increased until more solid food can be safely given. We have been very fortunate since inaugurating this procedure and, at the time of writing this paper, we have had no fistulae and relatively few infections. We feel that this manner of closing the pharynx and the elimination of the feeding tube have helped in avoiding factors that lead to a small tracheostoma.

In conclusion, the reasons for the difficulty in maintaining an adequate tracheostoma in laryngectomy cases have been given. In addition to the usual methods of constructing the stoma, the wider excision of skin and subcutaneous tissue, and the submucous resection of additional tracheal cartilage to give free tracheal mucosa for careful suturing of the skin to mucosa, are recommended. Closure of the pharyngeal opening with interrupted silk, and elimination of the use of the feeding tube postoperatively, are considered added factors in avoiding fistulae and infection which contribute to the eventual formation of an inadequate tracheal opening.

103 E. 78TH ST.

XXXVI

SURGICAL DECOMPRESSION OF THE RECURRENT
LARYNGEAL NERVE IN IDIOPATHIC UNILATERAL
VOCAL CORD PARESIS

PRELIMINARY REPORT

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Unilateral vocal cord paresis is termed idiopathic when none of the circumstances which are understood to be associated with trauma to the recurrent laryngeal nerve may be demonstrated. However, the condition seems to possess characteristics of a peripheral nerve lesion. Spontaneous recovery by the majority of patients from a lesion of a nerve peculiarly prone to degeneration after injury, suggested that many instances of paresis might be attributed to physiological block of transmission of nerve impulses. Accordingly, the anatomic relationships of the recurrent nerve were re-examined in order to discover whether or not, in the course of its distribution, it was particularly susceptible to compression, the most common mechanism of physiologic block. The cricothyroid articulation appears to provide a zone in which the anterior division of the recurrent nerve might course between rigid structures. Subperichondrial resection of thyroid cartilage could amount to decompression in this area.

This report, which is of a preliminary nature, is concerned with our experience with treatment of idiopathic unilateral vocal cord paresis by means of decompression of the anterior division of the recurrent nerve.

PRESENT CONCEPT OF VOCAL CORD POSITION
WITH RECURRENT NERVE PARALYSIS

Clerf and Suehs¹ have estimated that 90 per cent of recurrent nerve paralyses are of peripheral origin and 10 per cent have been

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ascribed to central lesions.² In most instances of unilateral paralysis, the specific local factors that have been stated to cause paresis are: diseases of the thyroid gland or injury to the nerve during thyroid gland surgery, severe trauma to the neck, cervical adenopathy, anterior mediastinal disease, aortic aneurysm, cancer of the esophagus, cardiac enlargement or lesions at the base of the skull. The remaining instances, for which no cause may be found, are called idiopathic. Various toxic and infectious agents have been stated to cause unilateral recurrent laryngeal nerve paralysis. Such instances of vocal cord palsy must be extremely rare. Lermoyez and Ramadier³ have stated that the hypothesis of peripheral neuritis is untenable. Frequently, cricothyroid arthritis is mistaken for idiopathic paresis and should be excluded by the passive mobility test at direct laryngoscopy.

There is considerable confusion in understanding the variations in position and tension of the vocal cord following injury to the recurrent laryngeal nerve. The midline, median or phonatory position all carry the same implication. This position according to Semon's Law,⁴ results with cases of paralysis of the abductor fibers of the recurrent laryngeal nerve.

The paramedian position leaves a space of 3 to 5 mm between the cords, and occurs with complete paralysis of the recurrent laryngeal nerve, when both the abductors and the internal adductor muscles are paralyzed. This position is influenced by the cricothyroid muscles which act as external adductors and rotators of the arytenoid cartilages.

Observations made by Clerf and Suehs on the position of the vocal cord during laryngectomy have shown that although the observations are brief, the cord assumes a midline position when the nerve is cut. It is incorrect to state that in cases of complete recurrent nerve paralysis the cadaveric position is taken up.

In the cadaveric or intermediate position, the glottic triangle measures about 7 mm. There is complete muscular relaxation and the position of the cord is assumed by virtue of the elasticity of the capsule of the cricoarytenoid joint. All of the muscles controlling the glottic margins are paralyzed, that is, the internal and external adductors and abductors. It is a position for recurrent nerve and

superior laryngeal nerve paralysis. In this state, the arytenoid is tilted forward, the cord occupies a lower position and the free edge is bowed.

In postthyroidectomy recurrent nerve injury, it is common to see cords in the paramedian position with lack of tension. With partial recovery, the cord may move to the midline. A cord has never been observed to move to the cadaveric position from the midline position.^{1,3} New and Childrey stated that a cord fixed in the midline may recover and that a cadaveric cord may move to the midline. However, these authors did not distinguish between paramedian and cadaveric positions.

Prognosis on recovery from the paralysis varies in the literature.¹⁻¹² New and Childrey⁵ found that with midline paralysis recovery may take 17 months, whereas with a cadaveric cord the recovery time was 10 months. Smith, Lambert and Wallace⁶ differed in that the majority of their cords were in the cadaveric position, and stated that New and Childrey were too optimistic in the outcome. Clerf and Suehs¹ reported complete recovery of the injured recurrent laryngeal nerve varies from as early as the sixth week to the third month. Muiligan⁸ on the other hand reports a poor prognosis in recurrent nerve paralysis following thyroidectomy in 17 cases. In 16 instances, paralysis of varying degree persisted for years.

The importance of the various positions of the vocal cord in unilateral paralysis may be summarized. The paramedian and midline paralysis may or may not recover. When the cord moves from the paramedian position to the midline position complete recovery is unlikely. The cadaveric or intermediate position with a bowed flaccid paresis indicates complete paralysis. Complete return of function is highly unlikely. The longer the period of paralysis, the less the chance of complete recovery. After one year, the chance for complete recovery is poor. Of particular importance is the susceptibility of the branches of the recurrent nerve close to the larynx to profound damage, especially to the fibers supplying the abductor muscles, in accordance with Semon's Law.

ANATOMIC BASIS FOR THE DECOMPRESSION PROCEDURE

The anatomical variations of the recurrent laryngeal nerve have been described by LeMere,^{10,11} Rustad,¹³ and others.¹⁴⁻¹⁶ Generally, the recurrent nerve courses superiorly more or less in the tracheo-

esophageal sulcus and gives off branches to these structures. The nerve is closely related to the inferior thyroid artery and to the posterior aspect of the thyroid gland. In 200 anatomical dissections of the nerve Rustad found that in 84 or 43 per cent of cadavers the nerve branched into several divisions in either one or both sides. Anatomy texts usually describe the anterior branch as passing superiorly along the crico-arytenoideus muscle to supply the lateralis, thyroarytenoideus, vocalis and aryepiglotticus muscles. The posterior branch is stated to supply the posterior cricoarytenoideus and the arytenoideus muscles.

The extralaryngeal divisions of the nerve are said to pass into the larynx posterior to the cricothyroid articulation. However, the anatomical illustration of Rustad and others of the extralaryngeal divisions of the recurrent nerve show the branches entering the larynx between the cricoid and thyroid cartilages, anterior to the cricothyroid articulation or immediately adjacent and posterior to the inferior cricothyroid articulation, to arc anteriorly between the thyroid and cricoid cartilages.

Observations made in the course of surgical dissections have impressed us with the considerable variation of the anterior division. The nerve enters the larynx immediately adjacent to the inferior thyroid cornu and is located between the thyroid and cricoid cartilages. The zone through which the nerve traverses between these two cartilages may be quite narrow, conceivably where it might be compressed.

Anatomic dissections of the recurrent nerves in four cadavers were performed to determine the relationship of the anterior division of the recurrent nerve to the cricothyroid articulation. Considerable anatomic variations of the cartilages and of the nerve were found. In one of four, the nerve was immediately adjacent to the cricothyroid joint in a particularly narrow zone. In the remainder, there was not only variation of the extralaryngeal nerves, but their entrances were distant enough from the cricothyroid articulation that compression would seem unlikely.

According to Murtagh and Campbell,¹⁷ the actual number of fibers injured will depend on the level of injury to the nerve. Relatively larger and more heavily myelinated fibers constitute the greater

number of fibers in the recurrent nerve and are concerned with adduction. Smaller and less myelinated fibers supply the abductor muscles. There is no histologic or physiologic evidence that the abductor fibers or adductor fibers are contained in separate bundles within the recurrent nerve.¹⁸

REPORT OF CASES

CASE 1. Sudden onset of hoarseness was experienced by a 15 year old boy about two weeks after a playful wrestling scuffle in which he had been subjected to an arm lock about his neck.

A complete medical and neurological workup was negative and the chest plate was negative. The left vocal cord was in a paramedian position. Weekly observations of the larynx were made and no vocal cord motion was observed for four months. After three and a half months' observation some lack of tone was evident but the cord did not assume a cadaveric position.

Since there was no sign of recovery after four months, the possibility that permanent damage had been sustained was considered. An alternative explanation was compression of a nerve anatomically susceptible to consequences of trauma at the time of the scuffle.

At the time of operation, there was no evidence of cartilage fracture, but the anterior division of the recurrent nerve was immediately anterior to the cricothyroid articulation, a narrow pathway. Electrophysiologic observation was made by stimulating this branch of the recurrent nerve, using 15 volts at 1 millisecond intervals. No movement was detected by laryngoscopy. There was no evidence of cricothyroid arthritis. Five days after surgery, distinct motion of the vocal cord was visible. By the tenth day full range of motion was observed. The voice returned to normal and the quality and range has remained excellent to date.

CASE 2. A 20 year old boy suddenly developed hoarseness without any injury or infection prior to the onset of the symptoms. There were no significant findings on examination except that the left vocal cord was fixed in the paramedian position. He was observed at weekly intervals. By the end of the fourth month the cord had moved to the midline, and the cord, previously in the paramedian position, now

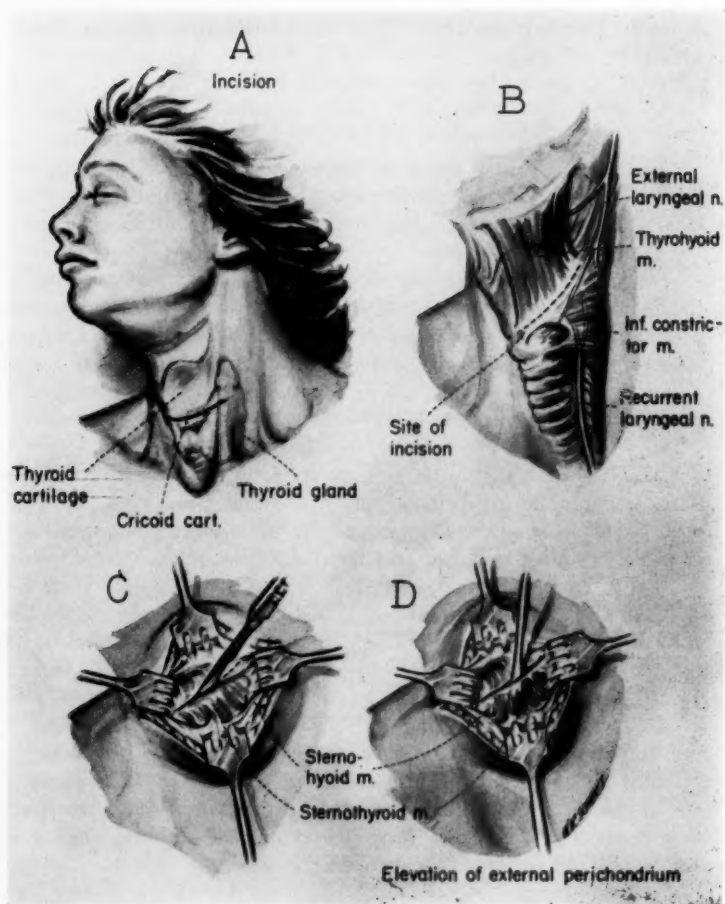


Fig 1.—Incision and exposure of thyroid cartilage. Site of incision (B) is over oblique line of thyroid cartilage.

appeared to have tension. The voice correspondingly improved but it was not normal.

At operation, the anterior division of the recurrent nerve was found immediately anterior to the cricothyroid articulation. Stimulation studies showed no movement of the vocal cord at laryngoscopy. Distinct movement was observed on the third postoperative day and full movement of the vocal cord and a normal voice were present on the tenth postoperative day.

CASE 3. A 45 year old white female with idiopathic right vocal cord paresis of nine months' duration was screened carefully for obvious causes. No evidence of cricoarytenoid arthritis was found. The right vocal cord was in the paramedian position. A thyroid cartilage decompression was carried out and observations of the cord were made for six months' period after surgery. No return of function was noted, and the voice quality remained the same as prior to surgery.

CASE 4. A 55 year old white male with hoarseness of one year's duration and idiopathic left vocal cord paresis was examined by direct laryngoscopy and bronchoscopy to rule out significant disease. No findings were found to suggest extrinsic causes. The vocal cord was in the paramedian position and tension was absent. The recurrent nerve was immediately posterior to the cricothyroid articulation. Decompression of the thyroid cartilage was performed and observation made for five months after surgery. No return of function was noted, and the quality of the voice remained the same.

TECHNIQUE OF OPERATION

Under local or general anesthesia, a small transverse incision approximately two inches long is made between the superior and inferior border of the thyroid cartilage on the side of the paretic cord (Fig. 1-A, B). After elevation of the skin flaps the ribbon muscles are separated longitudinally to expose the cricothyroid muscle. The thyroid lobe which covers the cricoid cartilage is reflected laterally to identify the anterior and posterior branches of the recurrent laryngeal nerve. In two of the four cases, the anterior division of the recurrent nerve entered the larynx through the cricothyroid membrane close to the cricothyroid articulation. In two others it was immediately posterior to the inferior horn. The oblique line of the

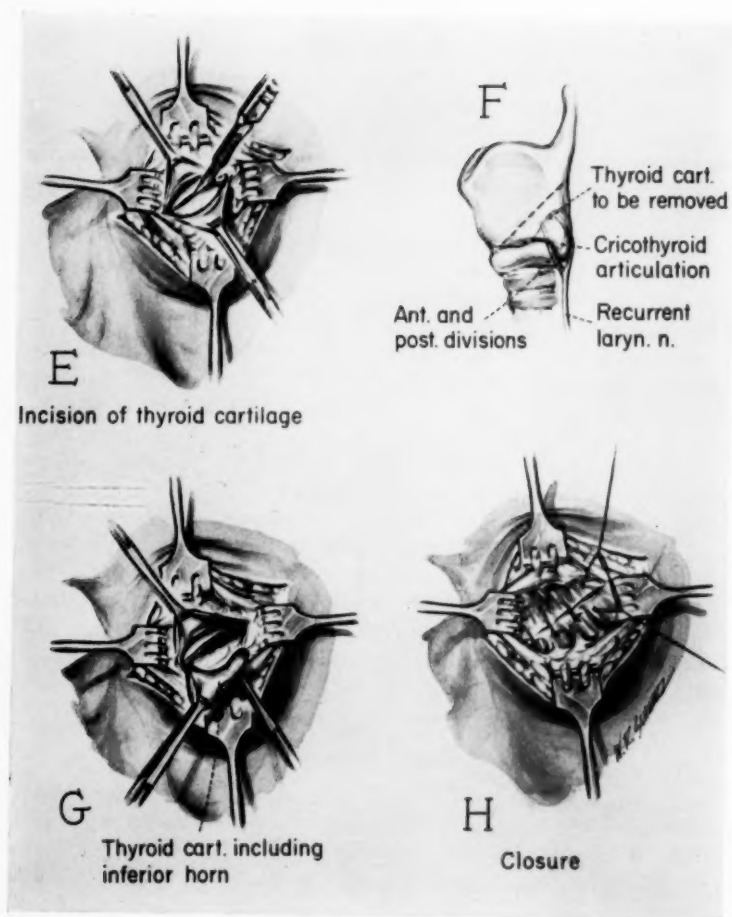


Fig. 2.—Removal of inferior triangular segment of thyroid cartilage. Anterior division of the recurrent laryngeal nerve (F) may be immediately adjacent or posterior to cricothyroid articulation.

thyroid cartilage can be identified on the thyroid lamina and the external perichondrium is incised along this line and elevated inferiorly (Fig. 1-C, D). The cartilage is next incised and a triangular segment of the thyroid cartilage, including the inferior horn, is excised after elevation of the cartilage away from its internal perichondrium (Fig. 2-E, F, G). The external perichondrium is approximated with silk and the skin and subcutaneous tissue approximated with interrupted silk (Fig. 2-H).

COMMENT

In the absence of any specific etiological factors, idiopathic recurrent laryngeal nerve paresis has remained an entity significantly free of surgical implications. In many instances, the cord in the paramedian position with lack of tone, may recover in two to three months. In other instances, the voice may improve when the cord moves to the midline, even though the cord may not regain motility. In some instances, partial recovery of abduction occurs. In rare instances, restoration of function has occasionally been observed after nine months or a year.

The recurrent nerve, particularly its anterior division, is stated to be one of the most vulnerable nerves in the body. General surgeons are aware of the frequency with which paresis of this nerve occurs even with gentle manipulation. The vulnerability of this nerve to trauma has been beautifully shown in experimental studies on dogs by Blalock and Crowe,¹⁹ and Judd, New and Mann.²⁰ Berlin⁴ feels that the variations of anatomic distribution of the nerve are more important than vulnerability. It should come as no surprise that pinching of this nerve between the thyroid and cricoid cartilages can occur with certain anatomic variations.

Electrophysiological studies made at the time of surgery on direct stimulation of the recurrent nerve could represent evidence of either physiological or anatomical interruption. The anatomic findings for compression of the anterior division of the recurrent nerve in two of the four cases, and the rapid return of motion in a previously paralyzed cord by decompression, would provide evidence for a physiological interruption. Unfortunately, electrical stimulation was not carried out immediately after decompression. When the exposed nerve was traced under the internal perichondrium for a short distance

toward the larynx, the nerve did not appear abnormal. However, I did not use magnification.

In one of the two cases that recovered function, the cord had moved to the midline prior to surgery, a finding indicating that spontaneous return of function was unlikely. Where decompression was carried out at four months after onset of paresis, mobility of the cord could be detected within five days.

In the two cases in which function was not restored, the paralysis had been present for nine or more months. Return of function is only rarely observed after paresis of this duration, and where nerve degeneration is probably permanent and regeneration is unlikely.

The permanent restoration to normal functioning cords after "early decompressions" appears to be very convincing. The procedure seems to have merits similar to the surgical decompression for Bell's palsy. Perhaps the spontaneous recovery rate in idiopathic paralysis is high, possibly as high as 75%. In these two cases one might argue that recovery was incidental and not attributable to surgical intervention. This is entirely possible. Larger experience will resolve this question.

In Bell's palsy, 85 per cent of the cases are reported to recover. In groups of various peripheral nerve injuries,²² spontaneous recovery occurred in 68 per cent of the cases, and the statement was made that this is better than that expected from suture repair.

Denny-Brown²³ in a beautiful piece of work demonstrated the effects of pressure, and of ischemia on peripheral nerves. He graded the findings in several degrees; paralysis with rapid recovery on release of pressure; paralysis with delayed recovery without degeneration (intermediate type of pressure lesion), and complete anatomic lesion with degenerative phenomenon. Even with the intermediate form of paralysis vacuolation of the axis cylinders and vacuolation of myelin was demonstrated. Degree of recovery was related to the total duration of pressure and paralysis, and recovery will be poorer, the longer pressure paralysis is allowed to persist.

More of the natural history of idiopathic unilateral paralysis and the frequency of partial and complete spontaneous recovery must be

learned. A larger series of cases should be studied with electrophysiological measurements. More extensive studies of the anatomic variations of the recurrent nerve and the cricothyroid articulation will permit evaluation of the hypothesis of compression as a factor in some cases of idiopathic unilateral vocal cord paresis.

SUMMARY AND CONCLUSION

A preliminary report is made of a surgical approach to the treatment of idiopathic unilateral recurrent nerve paresis. The surgical procedure was designed to relieve a postulated compression. The rapid return of function in two cases suggests that physiologic block was the mechanism of the paresis and tends to support the hypothesis of compression.

The possibility of a time factor is suggested by the successful outcome in the two cases operated on within five months of onset, while the two cases in which recovery did not occur were operated on more than nine months after onset.

The significance of these observations made on this operation for idiopathic vocal cord paresis will have to be deferred until greater clinical experience has been obtained.

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XXXVII

DEFICITS IN IRRADIATION THERAPY FOR

CARCINOMA OF THE LARYNX

FOLLOWED BY SURGERY

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Undoubtedly, there is some deficit in the expected end results when carcinoma of the larynx is treated by irradiation therapy and surgery is performed later. In all instances, surgery is done either because of irradiation necrosis, or incomplete control of the cancer. With the exception of some cases of far advanced cancer and those with metastasis, many cases treated by irradiation could likely have been treated by partial laryngectomy, total laryngectomy, or laryngectomy combined with radical neck dissection as the initial treatment. Some of these patients are treated by irradiation by choice of the laryngologist, and others at the request of the patient. Whenever tissues are subjected to irradiation, the capacity of the tissues to recover after surgical procedures is diminished.

Irradiation therapy for small cancers of the larynx, especially those of the true cords, is a recognized treatment today.¹⁻³ In some instances, irradiation therapy gives an over-all better result than does surgery. This depends to some degree on the ability of the surgeon, or the roentgen therapist, on the choice of treatment in relation to the grade of the cancer, the size of the lesion, and whether it is exophytic, or infiltrating. In some instances, for a few selected cases, surgeons prefer irradiation therapy of the lesion followed by surgery.

This paper is presented with several things in mind. In the last few years some very good papers have been presented regarding this subject.⁴⁻⁸ I wish to add to this so that an accumulation of cases

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may give us a better understanding, and make our selection of therapy be based on the individual case related to anatomy, pathology and physiology. There are several questions which I hope to answer in a review of these cases: What effect does the size of the field of irradiation have to do with future surgery of this area? Just what are the expected deficits as far as the cure of cancer is concerned when irradiation fails and surgery is done? What complications are to be expected in these cases? Since many of my cases have not survived five years following therapy, no conclusions can be drawn from actual survivals, but, must be based on experience and projected results.

The 23 cases, to be presented in group analysis, were from a series of 286 cancers of the larynx (Table I) treated since 1947, in four different institutions associated with the teaching program at Baylor University College of Medicine. Two types of radiation therapy were used: 220 K.V. (conventional apparatus), and 2 M.E.V. (Van de Graaff - electrostatic generator type). Though two or more therapists treated the cases using 220 K.V., the technique was essentially the same except for the size of the field and the variation of the dosage. All received 36 treatments over a period of approximately six weeks.

Those treated with 2 M.E.V. therapy were treated by the same therapist but were treated for a four-week period, or approximately 20 treatments over 28 elapsed days. They were given a smaller total dosage than the ones receiving treatment over a six-week period.

One hundred and twenty-four cases were operated upon either by laryngofissure, hemilaryngectomy, or laryngectomy with and without radical neck dissection. Forty-five cases had major surgical procedures and were irradiated because of local recurrence, or as an adjunct one month following surgery.

Twenty cases of early cordal lesion (limited in size to less than 1 cm in any direction and without fixation) were treated by either 220 K.V. or 2 M.E.V. therapy. Most of these cases were treated on the physician's recommendation.

Sixty-four cases were treated by either 220 K.V. or 2 M.E.V. irradiation. These were either considered to be lesions too large for surgery with distant metastasis or they refused surgery and accepted irradiation therapy as an alternate type of treatment.

TABLE I

	CASES OF CANCER OF LARYNX
Number of cases reviewed in this series	286
Number of patients operated by laryngofissure, hemilaryngectomy, laryngectomy with and without radical neck dissection and/or pharyngectomy and/or cervical esophagectomy	124
Number of patients operated by various major surgical procedures followed by irradiation because of local recurrence or as an adjunct one month after surgery	45
Number of cases of early cordal lesions or small lesions elsewhere in the larynx treated by x-ray	20
Number of patients treated by x-ray because they were inoperable or refused surgery	64
Number of cases that received x-ray treatment and later had some type of neck surgery	23
Number of patients who refused treatment or in whom cancer was too far advanced	11

Eleven cases were not treated either because they refused all types of treatment or were considered so far advanced that surgery or irradiation would be of no value.

Actually, then, the 23 cases operated upon following irradiation were from a group of 110 cases initially receiving x-ray therapy.

For the purpose of discussion, these 23 cases treated initially by irradiation therapy and later operated upon will be divided into four groups:

1. Cases of early carcinoma of the larynx less than 1 cm in any one direction, and without fixation (Table II).
2. Cases of advanced carcinoma of the larynx involving the true cords and endolarynx, larger than 1 cm and with fixation (Table III).
3. Cases of advanced carcinoma of the pyriform sinus, 2 cm or larger, but without metastasis (Table IV).
4. Cases of advanced carcinoma of the vallecula and epiglottis (Table V).

TABLE II

CASES OF EARLY CARCINOMA OF THE LARYNX LESS THAN 1 CM IN ANY ONE DIRECTION, AND WITHOUT FIXATION

AGE SEX	CHOICE OF TREATMENT	LOCATION OF LESION	GRADE OF LESION	PRE-OPERATIVE IRRADIATION	TYPE OF SURGERY	COMPLICATIONS	EXPECTED RESULTS
69 M	Phy. choice 1957	Lateral wall upper part pyriform sinus	II, well diff.	220 K.V., 5760 R., 6x6 cm Port, 36 treatments	4 months postoperative left radical neck 1957	4 months after sur- gery - Edema of Lar- ynx, Tracheotomy	Expected cure
41 M	Phy. choice 1959	Anterior third of right vocal cord	II, well diff.	220 K.V., 6200 R., 7x6 cm Port, 36 treatments	Early recurrence in thy- roid gland thyroidec- tomy healed 1960	After further radia- tion of neck necrosis no residual tumor on vocal cord	Death in 6 months
53 M	Phy. choice 1955	Anterior half of right vocal cord	II, well diff.	220 K.V., 6000 R., 6x5 cm Port, 36 treatments	18 months later partial laryngectomy & skin graft 1956	None	Well - Mar. 1961 Expected cure
57 M	Phy. choice 1952	Middle third of vocal cord	II, well diff.	220 K.V., 6000 R., 6x8 cm Port, 36 treatments	Recurrence of same area Laryngectomy 1960	None	Well - Mar. 1961 Expected cure
56 M	Phy. choice 1960	Anterior 1/3 of vocal cord	II, well diff.	220 K.V., 5800 R., 6x8 cm Port, 36 treatments	Recurrence in 6 months Laryngectomy 1961	None	Well - Mar. 1961 Expected cure
46 M	Phy. choice 1954	Middle third of vocal cord	II, well diff.	220 K.V., 5800 R., 6x8 cm Port, 36 treatments	Recurrence in 1960 - laryngofissure	None	Well - Mar. 1961 Expected cure
59 M	Phy. choice 1957	Anterior 1/2 of left vocal cord	II, well diff.	2 M.E.V., 5000 R., 4x6 cm Port, 4 weeks	Recurrence in 1960 - Laryngectomy	None	Well - Mar. 1961 Expected cure
42 M	Phy. choice 1959	Anterior 1/3 of right vocal cord	II, well diff.	2 M.E.V., 5480 R., 4x6 cm Port, 4 weeks	Recurrence in 6 months Laryngectomy	None	Well - Mar. 1961 Expected cure

TABLE III
CASES OF MORE ADVANCED CARCINOMA OF LARYNX INVOLVING THE TRUE VOCAL CORDS AND ENDO-LARYNX
LARGER THAN 1 CM AND WITH FIXATION

AGE SEX	CHOICE OF TREATMENT	LOCATION OF LESION	GRADE OF LESION	PRE-OPERATIVE IRRADIATION	TYPE OF SURGERY	COMPLICATIONS	EXPECTED RESULTS
55 M	Pt. choice 1950	Ant. $\frac{2}{3}$ of left vocal cord and ventricle	Well diff.	220 K.V., 5760 R., 6x6 cm, 36 treatments	Laryngectomy after 6 months	None	Well - Mar. 1961 Expected cure
46 M	Pt. choice 1957	Left vocal cord and adjacent area of ventricle	Well diff.	220 K.V., 6000 R., 5x6 cm, 36 treatments	Laryngectomy & left radical neck 3 months following irradiation	Fistula for about 4 weeks - beginning 1 month after surgery	Well - Mar. 1961 Expected cure
55 M	Pt. choice 1957	Ulceration of entire left cord	III, well diff.	220 K.V., 6500 R., 6x8 cm, 36 treatments	Laryngectomy & left neck - 5 mo. after irradiation	Area did not heal due to both irradiation and incomplete removal of cancer	Expired - 3 months after surgery
59 M	Pt. choice 1955	Both vocal cords and anterior commissure - Fixation	II, well diff.	220 K.V., 6500 R., 3.5 x4 cm, 36 treatments	Laryngectomy 6 months after irradiation	None	No follow-up since May 1958 Expected cure
60 M	Phy. choice 1955	Left vocal cord	II, well diff.	220 K.V., 6000 R., 6x6 cm, 36 treatments	Laryngectomy & left radical neck	None	Well - Mar. 1961 Expected cure
64 M	Pt. choice 1957	Anterior commissure and ant. half of both cords - No fixation	I, well diff.	2 M.E.V., 5500 R., 2.5x5 cm, 4 weeks	Laryngectomy & left radical neck specimen showed rad. necrosis and infection	Fistula midline occurred 12 days after surgery. Healed following 2 minor surgical procedures - 10 mos.	Well - Mar. 1961 Expected cure
65 M	Pt. choice 1950	Both vocal cords & base of epiglottis	II, well diff.	220 K.V., 7000 R., 8x8 cm, 8 weeks	Laryngectomy 6 months later	Tracheo-esophageal fistula	Expired - 6 months later
66 M	Pt. choice 1957	Entire left vocal cord with fixation	II, well diff.	2 M.E.V., 6000 R., 5x5 cm, 5 weeks	Laryngectomy 6 mos. after irradiation - 6 mo. later neck dissect.	None	Well - Mar. 1961 Expected cure

In group one, there are a total of 8 cases; all but one was of the true vocal cords. The one exception was a small lesion of the lateral wall of the pyriform sinus discovered accidentally. It might be noted that all of these were keratinizing type, or tumors well differentiated. The response to healing following surgery was about the same when 220 K.V. therapy was given as compared to 2 M.E.V.

Two were operated by laryngofissure and four by laryngectomy without complications. One was operated for a metastasis to the thyroid gland but there was no evidence of carcinoma in the larynx at postmortem. No doubt, the metastasis was present prior to therapy and would not have been altered by the type of surgery likely recommended. In one instance, a small pyriform sinus lesion was treated successfully by irradiation. Four months later a radical neck dissection was done for cervical node metastasis; prompt healing occurred. The disturbing complication was the marked edema of the larynx finally requiring a tracheotomy. Because of the persistent edema, decannulation was not accomplished for five months.

It might be noted that in no instance was the field of radiation larger than 6x8 cm and the amount of irradiation given was considered a cancericidal dose. All patients were given radiation therapy on the recommendation of the surgeon.

In the second group (Table III), there were eight cases, all with more advanced lesions, all involving the true cords and adjacent areas of the endo-larynx. Of these, four had wide field laryngectomy and four had laryngectomy with radical neck dissection. None of these showed clinical metastasis to the neck, but the radical neck dissection was done for subclinical metastasis. Four of the cases healed without complications and four developed fistulas, one in 12 days and the other in four weeks. In the one instance where the fistula developed in 12 days, the specimen showed no evidence of carcinoma but there was necrosis of the cartilage. Although the fistula was small, it required two small surgical procedures and ten months for complete healing. In the other case, the fistula healed spontaneously after one month.

In the other two cases, the lesion was more extensive than anticipated, and the fistula with necrosis and residual carcinoma resulted in death. In all of these cases, the field of irradiation was only slightly

larger than in the preceding eight cases, but the complications were greater.

It might be noted that all of these patients were irradiated at the patient's request. Only two of the cases have expired and, in the others, three to ten years have elapsed since the surgery was performed and there is no evidence of local recurrence.

In the third group (Table IV), only four cases of advanced pyriform sinus lesions were treated by irradiation, and all were treated by irradiation at the request of the patient. In three, a laryngectomy was performed, and in one a laryngectomy and radical neck dissection. Three expired within the first year. One, of a bronchogenic carcinoma without evidence of neck metastasis; one, with marked radiation necrosis and metastatic carcinoma beneath the clavicle. The third case healed well after surgery, but within 2 months developed a fistula, rupture of the carotid artery, hemiplegia and expired within six months of debility. No carcinoma was found at postmortem. The fourth case developed a fistula two weeks after surgery, but it closed spontaneously. This patient had a parotidectomy and neck dissection three years before for adenocarcinoma of the parotid gland.

Undoubtedly, in three cases, radiation added to complications after surgery but, due to metastasis and radionecrosis, only one of them survived for as long as one year. In the fourth case, there were no complications; however the patient expired in less than one year of a primary bronchogenic carcinoma.

In the fourth group (Table V), there were three cases all involving the epiglottis, the vallecula, and varying portions of the tongue. Two were irradiated on recommendation of the surgeon, and one on the patient's choice. In two there was good local response to irradiation; a radical neck dissection was done later for cervical metastasis. One died in ten months of generalized metastasis without evidence of local metastasis, and one is living and well four years later.

In the third case, irradiation was given on the recommendation of the surgeon; this case showed no evidence of carcinoma six months following surgery. Due to irradiation necrosis and hemorrhage, a laryngectomy and partial removal of the posterior third of the tongue was done. Healing was good for the first six weeks, but infection and

TABLE IV
CASES OF ADVANCED CARCINOMA OF PYRIFORM SINUSES 2 CM OR LARGER, BUT WITHOUT METASTASIS

AGE SEX	CHOICE OF TREATMENT	LOCATION OF LESION	GRADE OF LESION	PRE-OPERATIVE IRRADIATION	TYPE OF SURGERY	COMPLICATIONS	EXPECTED RESULTS
73 M	Pt. choice 1956	Large pyriform sinus lesion	II	220 K.V., 5000 R., 6x6 cm, 4 weeks	Laryngectomy	None	Expired - 9 months later of bronchogenic Ca. no recur- rence in neck
40 M	Pt. choice 1958	Large pyriform sinus lesion	II	2 M.E.V., 5000 R., 6x10 cm, 4 weeks	Laryngectomy, partial pharyngectomy, skin graft - 6 months after irradiation	Fistula - radio necro- sis metastasis beneath clavicle, no further surgery thought possible	Expired 6 months after surgery
60 M	Pt. choice 1957	Large pyriform sinus lesion with cellulitis of neck	II	2 M.E.V., 5500 R., 6.5x9 cm, 4 weeks	Laryngectomy and left radical partial pharyn- gectomy, skin graft 5 months after irradiation	Healed completely. Fistula formation two months later with rupture of com- mon carotid artery and ligation. 3 days later hemiparesis	Expired 9 months later, no carcinoma found at post- mortem
65 M	Pt. choice 1959	Two cm pyriform sinus lesion, left rad- ical neck and paro- tidectomy done for an adenocarcinoma 3 years before	II	2 M.E.V., 5000 R., 5x5 cm, 4 weeks	Laryngectomy 6 months after irradiation	Fistula - two weeks closed spontaneously	Patient well 9 months later, but cure ques- tionable

TABLE V
CASES OF ADVANCED CARCINOMA OF VALLECULA AND EPIGLOTTIS

AGE SEX	CHOICE OF TREATMENT	LOCATION OF LESION	GRADE OF LESION	PRE-OPERATIVE IRRADIATION	TYPE OF SURGERY	COMPLICATIONS	EXPECTED RESULTS
64 M	Phy. choice May, 1960	Ca. of vallecula of adjacent 1½ cm of tongue, no nodes in neck. Ca. of prostate 3 years before asymptomatic	II	2 M.E.V., 5000 R., 6x8 cm, 4 weeks	Laryngectomy 6 months later because of pain, hemorrhage and ulceration, no carcinoma found	Healed well until 4th week then ulcer- ation and necrosis became worse. Some hemorrhage at present	Prognosis poor will probably develop fistula
61 M	Pt. choice 1956	Ca. of epiglottis and left aryepiglottic fold	II	2 M.E.V., 6000 R., 6x8 cm, 5 weeks	4 months later left neck - 5 months later right neck, tumor in stri- ated muscle right neck	Healed well	March 1961 - No evidence of recurrence
66 M	Phy. choice 1952	Ca. of vallecula	II	2 M.E.V., 5000 R., 6x8 cm, 4 weeks	Left radical neck 6 months later	None	Died of general- ized metastasis 10 months later no evidence of local recurrence

ulcerations have continued in the pharynx and it is doubtful if the ulceration will heal, though no fistula has developed.

SUMMARY

Twenty-three cases of carcinoma of the larynx are reported which have had surgery following irradiation. These have been summarized into four groups: 1) early lesions of the vocal cords, less than 1 cm in size; 2) more advanced lesions of the vocal cords and endo-larynx; 3) advanced lesions of the pyriform sinus, 2 cm or larger; 4) advanced carcinoma of the vallecula and epiglottis.

All cases were given irradiation using a port as small as possible, keeping in mind that surgery might be done later. In none of the cases was a larger port than 8x10 cm used. In all cases a therapeutic dose of irradiation was given. In those cases where 220 K.V. was used, 36 treatments were given over a period of six weeks; the total tumor dose varied between 6000 R and 7000 R. When 2 M.E.V. was used and 20 treatments given, over 28 elapsed days, the tumor dosage varied between 5000 R and 6000 R.

CONCLUSIONS

1. The complications as a result of irradiation except in three cases was not great. It is doubtful if the end results would have been better had surgery been performed initially on those where irradiation necrosis took place.

2. The one striking observation is the rather high rate either recurrence, or lack of response to irradiation in the cases of group one. Here there was recurrence or lack of response in seven of twenty cases, and all of these showed well-differentiated carcinoma. In only two could a laryngectomy be averted. Though only one case has been lost in this group, it is likely death would have occurred had surgery been done initially. There is some deficit here, since a laryngectomy was done in four cases. Laryngectomy may have been prevented in these had a laryngofissure been done initially.

In the second group of cases, all should have had surgery by laryngectomy as the initial treatment, but in only one instance was it felt that surgery might have prevented death had a laryngectomy

been the initial treatment. The morbidity was relatively high in those who survived, because of complications which likely would not have developed had surgery been the initial treatment.

Except in two cases, in the third and fourth groups comprising seven cases, the patient chose irradiation. The end results have been poor and there has been complications in 50 per cent of the cases. In only two were they of such magnitude that pedicle flaps should have been done. Due to other factors, such as the general condition of the patient and distant metastasis, this was not carried out.

Finally, the deficits have not been great in cases of irradiation of the larynx followed by surgery, but it is certainly apparent that the larger the tumor and the field of irradiation the more likely complications will result if surgery follows the irradiation. In these cases, had the proper type of surgery been done initially three of the cases should have recovered, had not time been lost between the x-ray therapy and surgery.

One should weigh carefully the early lesions of the vocal cord in the well-differentiated cancer. Surgery should be considered since laryngectomy may be averted in some.

When irradiation is considered in advanced, but not inoperable, lesions, they should be considered future surgical candidates. By using as small a port as possible, when surgery does follow irradiation it certainly helps in the prevention of complications.

There seemingly is little or no difference in the response of the tissues to surgery when 220 K.V. as against 2 M.E.V. when the tumor dose remains the same, or a comparable dose is given depending on the number of elapsed days and the total number of treatments.

907 HERMANN PROFESSIONAL BUILDING

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XXXVIII

LARYNGEAL AND BRONCHIAL CANCER

A STUDY OF DOUBLE PRIMARY MALIGNANCY

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Multiple primary malignant tumors are becoming common clinical problems. Billroth¹⁴ described the first case in 1860, and numerous reports on the subject have appeared since that time. A careful definition of multiple primary malignancies is essential in order to differentiate a case of multiple primary tumors from one of a primary tumor with metastases. The rules formulated by Billroth appear too strict for practical purposes. He listed three criteria as essential in order to consider a case one of multiple primary malignant tumors: 1) each tumor must have a distinct, separate histologic identity; 2) the tumor must arise in different locations; and 3) each tumor must produce its own metastases. The first criterion is accepted without question. The third is not valid since often an unsuspected second primary tumor may not have metastasized. This is particularly true of a second silent tumor found incidentally during a post-mortem examination. The criteria of Warren and Gates¹⁴ are entirely adequate and practical from both a clinical and pathologic standpoint. According to these authors, in order to consider a case one of multiple primary malignancies, each of the tumors must present a definite picture of malignancy; each must be distinct and separate histologically; and the probability of one tumor being a metastasis of the other

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must be excluded. The only point of discussion in regard to this definition is the last part, "the probability of one tumor being a metastasis of the other must be excluded." If the tumors grow in different organs and have different histological patterns, there is no problem, even though one of them is a tumor of the lung. However, in a tumor with a varied histologic pattern as, for example, an adenocarcinoma with osseous elements—a so-called mixed tumor—metastases of only part of the tumor may be produced and these metastases may show a less or more mature pattern than the original tumor. But, careful histological study will show the difference between an atypical metastasis and a second primary malignant tumor.

INCIDENCE

It is very difficult to get a true impression of the frequency of multiple primary malignant tumors. Some of the statistical papers are based on findings of postmortem examinations in specialty hospitals. These statistics represent a selection according to the specialty of the hospital, whereas other statistics are based on clinical observations of patients being treated for cancer. Therefore, the incidence of multiple primary malignant tumors in the population as a whole varies from 0.3% to 7.8% in the recorded literature.^{14,15} The incidence of multiple primary tumors of certain organs appears to be far greater than that of the body as a whole. Wynder states that 157 or 11% of 1408 patients with carcinomas of the esophagus had or developed multiple primary carcinomas; this led to the statement that "the most well known pre-cancerous condition is cancer."

But while it is difficult to compare statistics of the incidence of multiple primary malignant tumors, it is even more difficult to correlate them with the mortality rates of the whole population. Only large series of cases could give an impression of the real status. Warren and Gates¹⁴ collected forty multiple primary malignant tumors among 1078 cancer-autopsies, and Warren and Ehrenreich¹⁵ continuing on the same studies found another 194 multiple primary malignant tumors in 2827 cancer autopsies. From these figures it appears certain that cases with multiple primary malignant tumors occur more frequently than could be expected on the basis of chance alone. The frequency of multiple primary malignant tumors observed in these two papers was six or seven to eleven times larger than might be anticipated by statistical calculation. While the figures may only

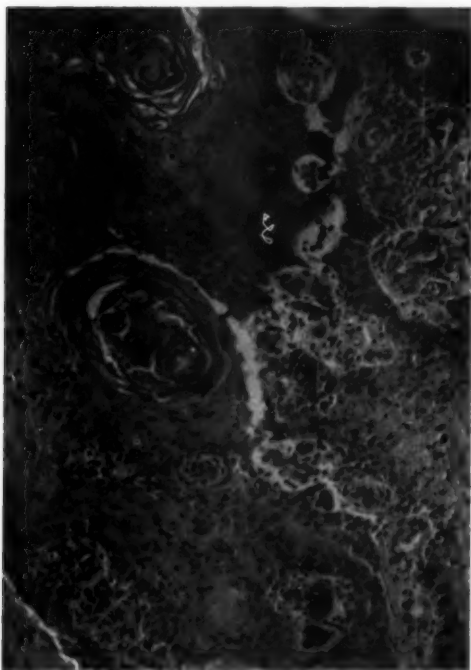


Fig. 1-A.—Photomicrograph of original laryngeal biopsy. The patient refused surgery (laryngectomy) and received a course of radiation therapy.

be approximate, the series are large enough to be of statistical significance.

The reports of Warren and Gates,¹⁴ Warren and Ehenreich,¹⁵ and Wynden¹⁶ show a tendency for multiple primary malignant tumors to occur in the same organ system, as for instance, in the skin, the gastro-intestinal tract or the genito-urinary system. Warren reported only one case of a primary tumor in the larynx and a second in the lung of the same patient, while Wynden added 6 cases of this double primary malignancy. He reported an incidence of 10% of multiple primary malignancies among larynx-cancer patients and an

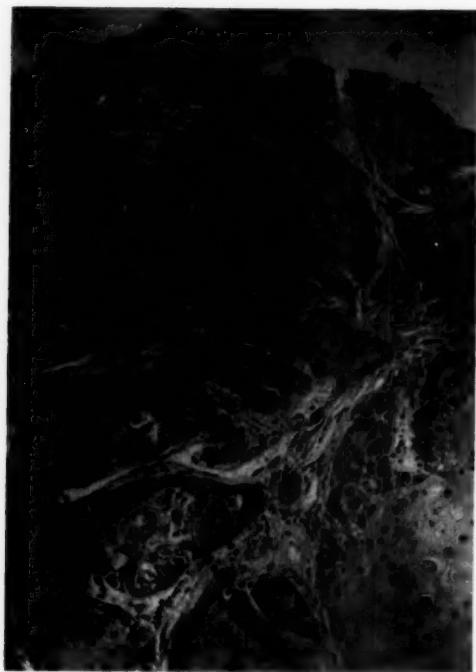


Fig. 1-B.—Photomicrograph of biopsy, Sept. 1955.

incidence of 13% of double primaries among lung-cancer patients, a greater frequency than would be expected from the general occurrence of multiple primaries. Of the six cases of larynx-lung multiple primaries reported by Wynden the first primary was the laryngeal lesion in 4, the bronchial lesion in one, and in one the two lesions were found simultaneously. Cahan, et al.,³ and Cahan² in studies of multiple cancers primary in the lungs and other sites collected a total of 23 cases with separate primary tumors in the larynx and the lungs. In 1956, Lewis and Schaff⁸ added 12 cases, Thompson and Schaff¹³ 7 cases, five of their own and two reported elsewhere, and in 1958, Rubenstein et al.¹¹ reported two additional cases. Thus, a review of

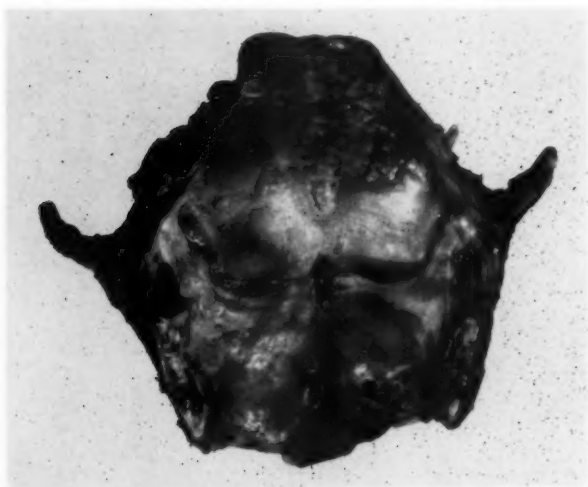


Fig. 2.—Laryngectomy specimen following biopsy shown in Figure 1-B.

the literature reveals a total of 51 cases of multiple primary malignant tumors involving the larynx and lung.

PRESENTATION OF CASES

This study is based on a series of 16 patients with primary malignant tumors in both the larynx and lung. The 16, all males, were between the ages of 42 and 71 years at the time of diagnosis of the first primary tumor; 3 were in the 4th decade, 5 in the 5th, 6 in the 6th, and two in the 7th decade. The average age was 58 years. In 14 of the 16 patients the lesions were metachronous with intervals of from 1 to 15 years, with the average interval of approximately 5 years. In two of the patients, the lesions were synchronous. In 11 of the 14 patients with metachronous lesions the cancer of the larynx preceded the cancer of the lung and in only three did the bronchogenic lesion precede the laryngeal cancer.

The therapy of the first primary lesion varied considerably in the 11 patients in whom the laryngeal carcinoma preceded the broncho-

TABLE I
LARYNGEAL AND BRONCHIAL CANCER: A STUDY OF DOUBLE PRIMARY MALIGNANCY

NO.	INIT.	AGE (ALL MALES)	1ST PRIMARY		INTER- VAL (YRS.)	2ND PRIMARY		THERAPY	PRESENT STATUS
			SITE	THERAPY		SITE	THERAPY		
1	PB	60	Lung left lower lobe	Pneumonectomy	2 3/4	Larynx vocal cord	Refused	Refused	Lost to follow-up.
2	JW	71	Lung right main bronchus	Pneumonectomy	3	Larynx left cord with metastases	X-ray		Living with disease 5 yrs. after 2nd primary. Lost to follow-up thereafter.
3	RN	51	Larynx vocal cord	Thyrotomy and Cordectomy	5 1/2	Lung Rt. lower lobe with metastases	Nitrogen Mustard		Died 2 months later. Br. Ca. metastases. No malignancy in larynx site or neck.
4	CK	65	Larynx left cord	Laryngectomy	5 1/2	Lung rt. main bronchus	Nitrogen Mustard		Died 2 months later. Br. Ca. metastases. No malignancy in larynx site or neck.
5	FW	55	Larynx left cord	Cordectomy; laryngectomy 4 yrs. later	4 1/2	Lung left main bronchus	Pneumon- ectomy		Living 1 year later. Lost to follow-up thereafter.
6	EF	60	Larynx right vocal cord	Laryngectomy	2 1/2	Lung left main bronchus	Nitrogen Mustard		Died 2 months later. Br. Ca. metastases. No malignancy in larynx site or neck.
7	AD	57	Larynx left vocal cord	Laryngectomy	5 1/2	Lung left main bronchus with metastases	Nitrogen Mustard Cobalt		Died 2 months later. Br. Ca. metastases. No malignancy in larynx site or neck.

8	TL	49	Larynx left cord	X-ray laryngectomy	4 1/2	Lung lef main bronchus	Pneumon- ectomy	Living, no evidence of carci- noma 2 years after pneumon- ectomy.
9	LL	51	Larynx vocal cord	X-ray Laryngectomy Radical Neck	3	Lung right lower lobe	Lobec- tomy	Died 3 months later. Br. Ca. metastases. No malignancy in larynx site or neck.
10	ZT	42	Epiglottis	Laryngectomy and Bilat. Rad. Neck	1 1/2	Lung right lower lobe	X-ray (Pallia- tive)	Died 2 months later. Br. Ca. metastases. No malignancy in larynx site or neck.
11	JB	61	Epiglottis	Laryngectomy	0	Lung left lower lobe	Lobec- tomy	Living and well 1 year post surgery.
12	CG	54	Trachea and Bronchi	Endoscopic Re- section, Radon, External radiation	7	Larynx left vocal cord	None	Died following malignant tracheoesophageal fistula.
13	LR	69	Epiglottis	Laryngectomy and Rt. rad. neck	2	Lung left	Pneumon- ectomy	Still under treatment.
14	NT	72	Larynx right vocal cord	Laryngectomy and Bilateral neck	0	Lung right upper lobe	Pneumon- ectomy	Living, no evidence of carci- noma.
15	FB	44	Epiglottis and base of tongue	X-ray	15	Lung left upper lobe	None	Died of cerebral metastases of br. ca. No evidence of tumor larynx or neck.
16	GF	61	Larynx right cord	Thyrotomy and Cordecotomy plus x-ray therapy	6 1/2	Lung right upper lobe	Resection (incom- plete)	Still under treatment.

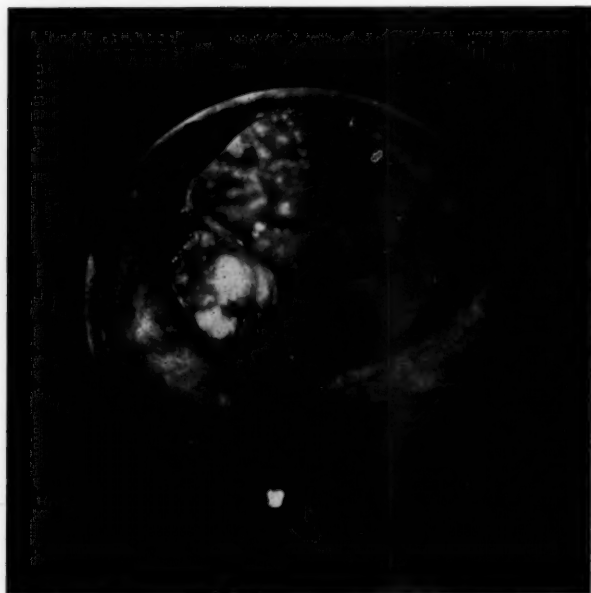


Fig. 3.—Endoscopic photograph of tumor in left main bronchus.

genic carcinoma. Three had a thyrotomy and cordectomy. In one of the three, a laryngectomy was performed four years later for local recurrence and in one the surgery was followed by x-ray therapy; he had no local recurrence when the bronchogenic carcinoma was found six and one-half years later. In three patients the initial therapy of the laryngeal carcinoma was radiation. One had an extensive, inoperable carcinoma of the epiglottis that responded dramatically to radiation. He had no local recurrence when he died fifteen years later of what postmortem examination demonstrated to be cerebral metastases of a small cell bronchogenic carcinoma. One patient (Figs. 1-5) refused surgery on discovery of the laryngeal carcinoma and received a course of x-ray therapy, but because of local recurrence five months later, agreed to total laryngectomy; his bronchogenic carcinoma was

discovered four and one-half years later after the initial diagnosis of the laryngeal cancer. The bronchogenic tumor was treated by total pneumonectomy. In the third patient in this group whose initial therapy consisted of irradiation, the tumor recurred locally one year later and a laryngectomy was performed. Within another year, a contra-lateral neck dissection was done for a metastatic cervical node. Three years later a small cell bronchogenic carcinoma was found. This was resected by a lobectomy since at the time of surgery non-resectable mediastinal metastases were evident. Postmortem examination four months later showed no residual or regional carcinoma that could be considered due to the original laryngeal lesion. In three of the seven patients in whom the initial primary tumor was the laryngeal lesion, a total laryngectomy was performed, and in the remaining two of this group, a laryngectomy and unilateral neck dissection were performed in one and a laryngectomy and bilateral neck dissection were performed in the other.

The therapy of the first primary lesion of two of the three patients in whom the bronchial tumor preceded the laryngeal carcinoma consisted of a total pneumonectomy. The laryngeal lesion in each of these appeared approximately three years after the bronchogenic carcinoma. In one, a laryngectomy and radical neck dissection were recommended because of the extent of the laryngeal carcinoma. His general condition would not permit this surgery and he received palliative radiation therapy only. The second patient had an early laryngeal lesion involving the left vocal cord three years after a pneumonectomy. There were no cervical nodes and the cord was freely movable. X-ray therapy was recommended but the patient refused all therapy and has been lost to follow-up. The third patient in whom the bronchial carcinoma preceded the carcinoma of the larynx actually had a carcinoma of the trachea at its bifurcation with ultimate extension into both the left and right bronchi. The tracheal and bronchial lesions were treated by fulguration and electroresection, radon seed implantation and external irradiation. Seven years after the initial tumor had been identified, a separate, isolated and histologically distinct laryngeal neoplasm was found on the left vocal cord. Because of the mediastinal and bronchial extent of the tracheal lesion no therapy was considered nor indicated for the laryngeal lesion other than endoscopic excision as palliation. He died shortly thereafter following esophageal extension into the mid-thoracic esophagus and the development of a large tracheo-esophageal fistula.

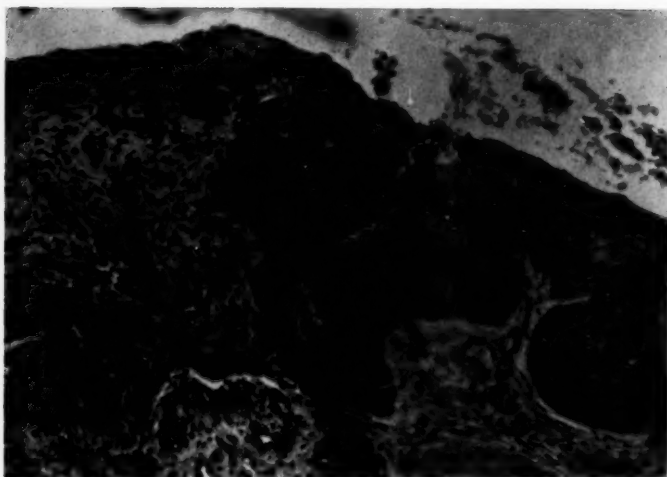


Fig. 4.—Photomicrograph of biopsy of tumor of left main bronchus.

In five of the eleven patients in whom the bronchogenic carcinoma was the second primary malignant tumor, the therapy of the pulmonary lesion was surgical. Three had total pneumonectomies, and two a lobectomy. Three of the remaining six received nitrogen mustard alone, one received nitrogen mustard followed by Cobalt therapy, the fifth received palliative irradiation alone, and in the sixth, the bronchogenic tumor was found on postmortem examination fifteen years after diagnosis and treatment of the laryngeal lesion. As stated above, it was responsible for sudden coma and death prior to clinical examination or diagnosis.

In two patients the laryngeal and bronchial lesions were synchronous. One, 61 years of age, was found to have a squamous cell carcinoma of the epiglottis. Medical and x-ray studies preceding a laryngectomy disclosed a density in the left lower lobe and a bronchoscopic biopsy showed the lesion to be a small-cell bronchogenic carcinoma in the left lower lobe bronchus. In view of the greater potential danger of the broncho-pulmonary lesion, a left lower lobectomy was performed first and a month later the laryngectomy was done.

This patient's history is of further interest in view of a third primary lesion involving the base of the tongue nine years preceding the discovery of the epiglottic and bronchial tumors. Exploratory pharyngectomy had shown this lesion to be inoperable. It was treated by radon seed injection, followed three weeks later by a bilateral neck dissection. Thus, the laryngectomy was performed nine years following a bilateral neck dissection, a rather unusual surgical exercise. While the tumors of the base of the tongue and the epiglottis may be considered to have been in some proximity, the epiglottic lesion was localized to the tip and posterior surface of the epiglottis and did not extend into the vallecula nor the tongue. The laryngeal lesion in this patient, a squamous cell carcinoma, and the bronchogenic tumor, a small cell carcinoma, were of distinctly different cell types.

The second patient in whom the lesions were synchronous was a 72-year old white male whose symptoms were hoarseness of one month's duration, an eighteen-pound weight loss, anorexia, and a productive cough with occasional blood streaking. The mirror examination of the larynx demonstrated an ulcerating mass involving the base of the epiglottis and extending along the right true and false cords. A chest x-ray revealed a mass in the anterior portion of the right upper lobe. Respiratory obstruction necessitated a tracheotomy following which the laryngeal biopsy could be obtained; the lesion was an epidermoid carcinoma. A bronchoscopic examination did not disclose the point of bronchial origin of the right upper lobe tumor but demonstrated compression of the anterior segment of the right upper lobe bronchus. A thoracotomy was performed ten days following the tracheotomy and the tumor found to be adherent to the chest wall, compressing the right pulmonary artery and right bronchus necessitating a total right pneumonectomy. A month later a total laryngectomy and right radical neck dissection were performed with histologic evidence of epidermoid carcinoma in two of 24 cervical nodes but none in the scalene nodes. The only immediate complication of either of these surgical procedures was a pericarditis following the pneumonectomy. Three weeks following the laryngectomy and right neck dissection a node was palpated over the left carotid bifurcation and a left radical neck dissection was performed, with carcinoma demonstrated in 4 of 21 nodes. The patient remained hospitalized for six weeks, being discharged from the hospital 3½ months after admission with no further evidence of malignancy.



Fig. 5.—Gross surgical left pneumonectomy specimen, Dec. 1959.

in either the neck or chest. The similarity of the histology of the two lesions in this patient raises the question as to whether the pulmonary mass was a metastasis of the primary laryngeal carcinoma. The apparent bronchial origin of the tumor in the resected lung is a strong indication that this lesion was a second primary malignancy.

COMMENT

The difference in degree of malignancy between laryngeal and bronchial carcinoma is apparent in the clinical course of these 16 patients. Eight of the 16 have died of their bronchial carcinomas with no evidence of regional or systemic metastases of the laryngeal lesion. One who had a thyrotomy and a cordectomy in 1948, a laryngectomy in 1952 and a pneumonectomy in 1953, was living and free of disease in 1954, but has since been lost to follow-up. The two patients treated by pneumonectomy whose bronchogenic carcinoma preceded the laryngeal carcinoma are presumed dead. In each the laryngeal tumor followed the pneumonectomy by approximately three years. One refused all therapy at the time of diagnosis of the laryngeal tumor in 1947 and has been lost to follow-up. The second, 74 years of age in 1949 at the time of diagnosis of the laryngeal

lesion, had a left vocal cord carcinoma with cervical metastases. He received x-ray therapy, was known to be living five years later but his medical status was unknown, and he, too, has been lost to follow-up since that time.

Five of the sixteen patients are still living. Two are the patients in whom the lesions were synchronous and their histories are given above. Both are living and apparently free of carcinoma but the diagnosis and treatment of each has been affected within the past year. Two patients whose bronchial lesions appeared two, and six and one-half years after the laryngeal tumor have only recently been operated and are still under postoperative management. One had a pneumonectomy and one a partial pneumonectomy including several ribs; the extent of the rib invasion permitted only an incomplete resection. The fifth patient still living is apparently free of carcinoma; however, he had a severe coronary occlusion in the postpneumonectomy period, one and one-half years ago.

SUMMARY

This report records sixteen additional cases of multiple primary carcinomas involving the larynx and bronchi. The two lesions in each patient were separate histologically and were metachronous in fourteen, separated by an interval of from one and one-half to fifteen years. They were synchronous in two patients in whom the bronchial lesions were discovered during the medical survey preceding surgery for the laryngeal carcinoma. The laryngeal tumor preceded the bronchial tumor in 11 of the 14 in whom the tumors were metachronous and in the remaining three the bronchogenic tumor preceded the laryngeal carcinoma.

All patients were males between the ages of 44 years and 71 years. Therapy of the 11 whose first primary involved the larynx consisted of thyrotomy and cordectomy and in three followed by x-ray therapy in one and a laryngectomy in one. Three had irradiation for the laryngeal primary; in one the tumor had been considered inoperable, one refused surgery but required a laryngectomy five months later for residual laryngeal carcinoma and one had a lesion that appeared suitable for radiation therapy but he required a laryngectomy and a radical neck dissection a year later. In the remaining five patients the therapy of the primary laryngeal tumor was a total

laryngectomy in three, a laryngectomy and unilateral neck dissection in one and a laryngectomy and bilateral neck dissection in the other.

The therapy of the second primary, the bronchogenic carcinoma, in the 11 patients in whom the laryngeal tumor preceded the bronchogenic carcinoma, was as follows: In five only palliation was possible and consisted of nitrogen mustard and irradiation; no therapy was possible in a sixth. All six have died with metastases of the bronchial lesions and without evidence of local or regional recurrence of their laryngeal lesions. Pneumonectomies were performed on three, each of whom had had a laryngectomy. A lobectomy was performed on one patient who had had a previous laryngectomy and radical neck dissection. A partial lobectomy and rib resection for invasive carcinoma was performed on the eleventh patient who had had a thyrotomy and corpectomy followed by radiation six and one-half years before.

Two of the three whose bronchogenic lesion preceded the laryngeal cancer were treated for the first primary by pneumonectomy; the third whose lesion originated at the tracheal bifurcation and advanced to the bronchi was treated by local resection and irradiation. The second or laryngeal carcinoma was untreated in two; in one the laryngeal carcinoma was an incidental pre-terminal finding and the second refused therapy and was lost to follow-up. The laryngeal lesion in the third patient was far advanced with regional metastases when the diagnosis was established and only palliative irradiation was possible because of his poor general condition.

The two patients in whom the lesions were found simultaneously, one had a lobectomy and one a total pneumonectomy, the laryngeal surgery in each being performed one month later. One had had an inoperable carcinoma of the base of the tongue treated by radon seed implantation and bilateral neck dissection nine years previously. He has no evidence of residual or metastatic carcinoma from either of the three primary lesions. The second had a pneumonectomy and one month later a laryngectomy and radical neck dissection. Three weeks later a neck dissection was performed on the opposite side.

The sixteen cases of primary carcinoma in both the larynx and tracheobronchial tree herein presented support the evidence of organ susceptibility to cancer. They demonstrate, too, the far more serious malignant potential of bronchogenic carcinoma than cancer of the

larynx. And finally, this study emphasizes the statement that the most serious pre-cancerous lesion is cancer.¹⁷

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The Scientific Papers of the American Otological Society

XXXIX

STUDIES ON THE EFFERENT INNERVATION OF THE VESTIBULAR END ORGANS

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The transmission of nerve-impulses in the labyrinth has been an important physiological problem for some time. Much knowledge was obtained by electro-physiological methods about the function of both the cochlear and the vestibular end-organs. Recently the existence of a system of cholinergic nerve fibers has been demonstrated in the organ of Corti by Schuknecht and in the vestibular receptors by Dohlman. It is the purpose of our experiments to find additional information regarding the vestibular cholinergic mechanism.

Histochemical experiments of Schuknecht and Churchill showed that acetylcholin, together with the enzyme acetylcholin-esterase, is present in nerve fibers and nerve-endings of the organ of Corti, probably mediating the chemical transmission of the impulses in some synaptic regions of the cochlea.¹ It may be assumed that the cholinergic nerve endings during nerve stimulation release acetylcholin which, after acting as transmitter substance, is hydrolized by the enzyme

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acetylcholin-esterase in a very short time, then resynthesized and stored in the axoplasm. Quantitative determination of acetylcholin-esterase shows that the concentration of this enzyme runs parallel with acetylcholin in any given section of the central or peripheral nervous system, indicating the close relationship of these two substances. Thus, both the enzyme and its specific substrate are essential for this physiological process.

There is experimental evidence that the cochlear cholinergic mechanism is efferent.² Intramedullary division of the olivo-cochlear bundle was followed by degeneration of this tract and disappearance of the enzyme, acetylcholin-esterase in the cochlea; consequently it appears to be related to the efferent fibers of the anatomically well-known tract of Rasmussen. As stimulation of this tract depresses the action potentials of the acoustic nerve, it represents an inhibitory feedback pathway by which central impulses modulate the peripheral cochlear responses.

The cholinergic innervation is not restricted only to the auditory part of the membranous labyrinth. Efferent nerve fibers are demonstrated by the same histochemical method in the vestibular cristae of the pigeon.³ High acetylcholin-esterase activity is present under the neuro-epithelium of the semicircular canals indicating the presence of such fibers, the function of which is however still unknown.

In our present series of experiments we have tried to investigate further the existence and function of the vestibular cholinergic mechanism in different species of mammals, and its distribution in the end-organs of the non-auditory membranous labyrinth. For this purpose we used the histochemical method of Koelle-Friedenwald, which shows the areas of increased acetylcholin-esterase activity. This method is based upon the enzymatic hydrolysis of the thioanalogue of acetylcholine by its specific enzyme, acetylcholin-esterase. The tissue is left incubating in a buffered medium containing the substrate and cupric ions. The liberated thiocholine precipitates as copper thiocholine and is converted to stable copper-sulphide in the last phase when the specimen is placed in ammonium-sulphide solution. Darkish brown precipitate, copper-sulphide is then visible at the sites of acetylcholin-esterase activity.

We thought that if the vestibular cholinergic innervation is efferent, then section of the VIII nerve, leaving at the same time the

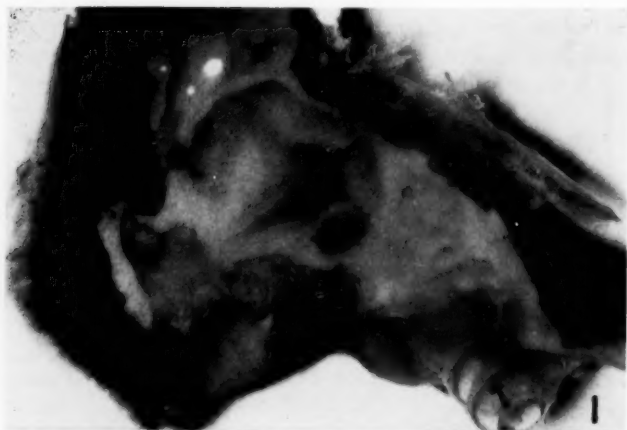


Fig. 1.—Guinea pig labyrinth, vestibulum and last two turns of cochlea opened. Dark copper-sulphide precipitate in the cristae of the superior and lateral ampulla and along the organ of Corti. Koelle-Friedenwald technique.

blood supply of the labyrinth undisturbed, would cause only degeneration of this system of nerve fibers. The vestibular ganglia and neuro-epithelial cells would remain intact. Intracranial division of the auditory nerve has already been performed by Rasmussen and Gacek⁴ who were able to prove by this method the presence of efferent fibers in the vestibular nerve.

METHOD

Nine cats and five guinea pigs were used in the experiments. The animals were anesthetized by intraperitoneal Nembutal, the auditory bullae opened and the basal turn of the cochlear snail entered through a small burrhole. Thereafter the stapes was luxated or in some experiments the lateral canal was fenestrated to produce a counter-opening on the bony labyrinthine capsule. A small polyethylene tube of adequate diameter was then inserted in the burrhole in the scala vestibuli and the vestibular labyrinthine spaces were intravitaly perfused with the specific substrate solution, containing acetyl-thiocholine in glycine buffer, saturated with copper thiocholine. This was



Fig. 2.—Guinea pig, neuro-epithelial area from the crista ampullaris. Precipitate localized to subepithelial region and nerve-fibres, not in hair-cells.

left incubating for 30 minutes in the labyrinth, which was thereafter rinsed with distilled water, containing cupric ions. Finally the labyrinthine spaces were perfused with 1 per cent ammonium-sulphide which again was left for some minutes. Subsequently the tissues were intravitaly fixed by 10 per cent formalin perfusion. In a few animals the cochlea was also perfused with these solutions by the same route, a small burrhole at the apex serving as an outlet. The animals were sacrificed, the temporal bones removed, decalcified in trichloracetic acid and the sections counterstained.

In seven cats, the auditory nerve was first completely divided on one side. In Nembutal-anesthesia the occipital squama was widely resected, the transverse sinus ligated and the dura of the posterior

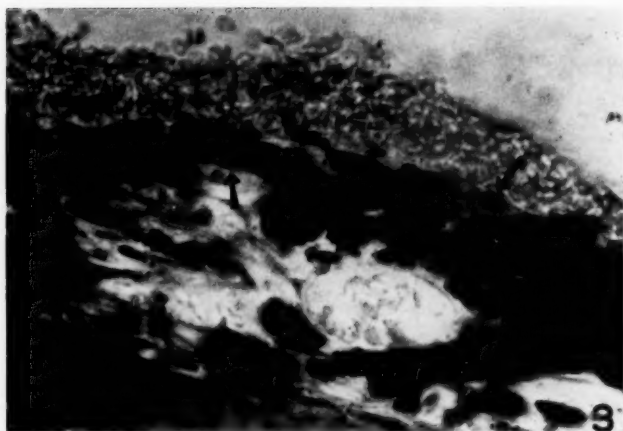
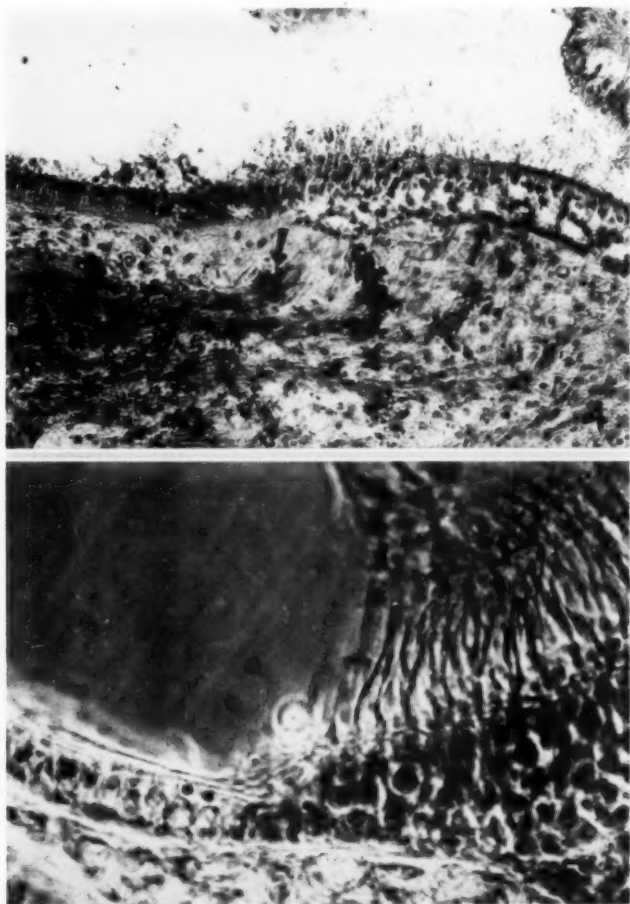


Fig. 3.—Guinea pig, crista ampullaris. Dense copper-sulphide precipitate along nerve-fibres, showing increased acetylcholin-esterase activity.

fossa opened. After removing a generous amount of C.S.F. by suction, the cerebellar hemisphere was gently displaced medially. The roots of the VII-XII cranial nerves were thus well exposed and the thick white tract of the auditory nerve was divided with the fine tip of a glass suction tube as close to the medulla as possible. Special care was taken not to disturb the blood supply of the labyrinth. The posterior inferior cerebellar artery was distinguishable in most animals, caudal to the VIII nerve, hugging the lateral surface of the medulla and sending an anastomotic branch anteriorly over the dorsal aspect of the nerve. The internal auditory artery, the sole arterial blood supply to the labyrinth was found adherent to the ventral surface of the auditory nerve. However, in two animals, the artery entered the nerve close to the medulla and ran among the nerve fibers. In these cases it was involuntarily divided together with the nerve. The animals were allowed to survive for 6 to 8 weeks, i.e. the period necessary for the Wallerian-degeneration to develop. Thereafter, the histochemical procedure was performed on both labyrinths as discussed above, thus rendering it possible to compare the reaction of the operated side with that of the intact VIII nerve in the same animal.



Figs. 4-5.—Cat 6, sacrificed seven weeks after division of auditory nerve on one side.

Fig. 4.—Nonoperated side, ampullar crista. Copper-sulphide precipitate in characteristic sites.

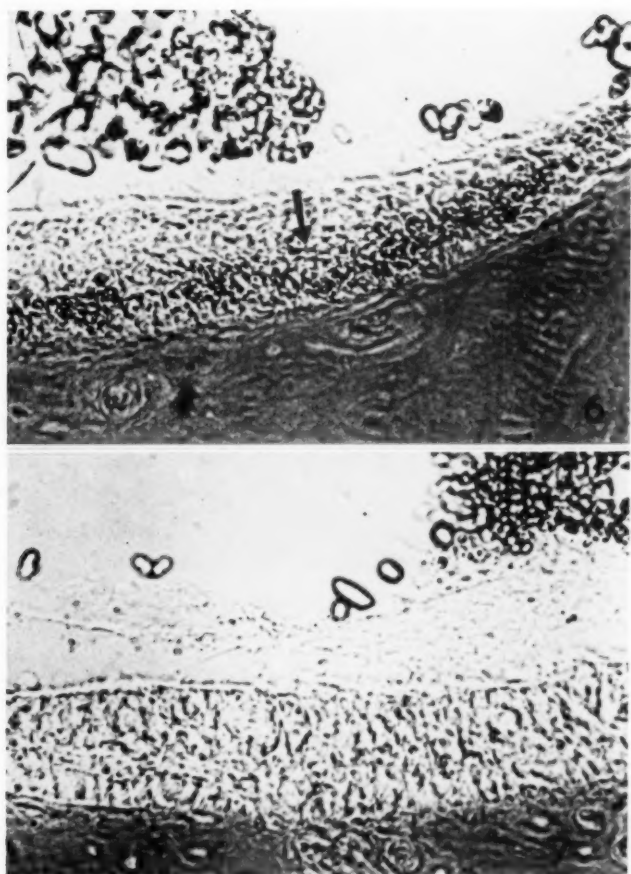
Fig. 5.—Operated side, ampullar crista. No precipitate visible. No signs of end-organ degeneration, as the blood-supply was left intact.

Striated muscle sections were also run parallel with the labyrinthine specimens through all the different phases of the histochemical method, but at occasions not exposed to the specific substrate. To verify the type of the reacting cholin-esterase 5×10^{-6} M Prostigmin solution was used as inhibitor so that nonspecific cholin-esterases would be inactivated. Also some specimens were incubated with butylcholin solution with and without inhibitor.

The electron micrographs show the structure of the vestibular end-organs of the guinea pig. The labyrinths of these animals were intravitaly perfused with chilled, buffered osmic acid solution through a small burrhole in the basal turn of the cochlear snail, the stapes being previously luxated to provide outlet for the perfusion fluid. Thereafter the animals were sacrificed, the petrous bones removed, placed in osmic acid solution for further fixation for three hours, the membranous labyrinth dissected free and processed by the current routine electron microscopic technique.

RESULTS

Copper-sulphide is precipitated in the final phase of the Koelle-Friedenwald method on the sites of acetylcholin-esterase activity. This characteristic reaction occurred also in the vestibular end-organs (Fig. 1). When the outer bony wall of the vestibule was removed, dark brown precipitate became visible in the ampullae of all three semicircular canals and in the utricle. The reaction was less marked in the saccule, probably due to the fact that its macula lies more hidden in the bony groove and the incubation medium reagents could not penetrate there to produce adequate concentration at the enzyme site. In both the ampullae and the utricle the precipitate was localized to the receptor areas and thus in the vestibular cristae and macula. It appeared to be evenly distributed in both areas forming a dark halfmoon shape in the ampullae and a broad dark area under the white layer of otoconia in the utricle. No significant difference was found between the two sides of the cristae, that is, towards and away from the utricle. In the specimens where, through a counter opening on the apex the cochlea was also perfused, deep dark stripes showed along the spiral osseous lamina in all the turns where the specific substrate came into contact with the organ of Corti. The controls did not have this precipitate neither on gross nor microscopic examination.



Figs. 6-7.—Cat 7, sacrificed 48 days after operation.

Fig. 6.—Nonoperated side, utricular macula. Note the localization of precipitate in the subepithelial area, not in the hair-cells themselves.

Fig. 7.—Operated side, utricular macula. No precipitate.

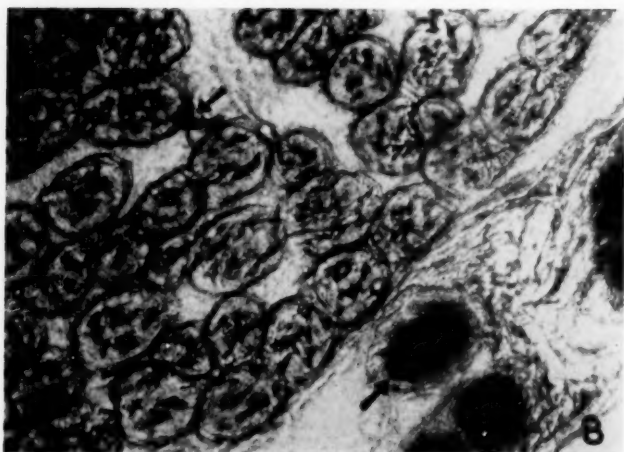


Fig. 8—Cross-section of striated muscle. Copper-sulphide precipitated in motor-nerve fibers and neuromuscular endplate.

Microscopic sections of the vestibular end-organs show that the precipitate, i.e. the acetylcholin-esterase activity is confined to the subepithelial region of the receptors, that is, to the nerve endings and nerve fibers below and between the hair cells (Fig. 2). Sometimes heavy sedimentation is visible a little farther from the receptor area in the vestibular nerve branches themselves where the acetyl-thiocholine crystals were not quite transformed to copper-sulphide in the last phase indicating strong enzyme concentration along these fibers (Fig. 3).

Two of the seven cats which had their auditory nerve divided prior to the histochemical process showed complete degeneration of the cochlear and vestibular end-organs due to involuntary division of the internal auditory artery. These were not available for study. The remaining animals all showed more or less markedly the characteristic histochemical reaction in the vestibular end-organs of the nonoperated side while the operated side was free from any precipitate (Figs. 4 to 7).

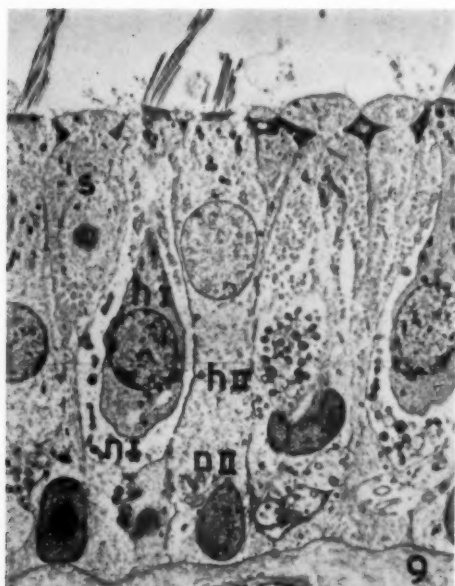


Fig. 9.—Electron-micrograph, guinea pig, crista ampullaris showing the two types of vestibular hair-cells and nerve-endings. Short, flask shaped neuro-epithelial cell (H₁) surrounded by a single nerve chalice (N₁). Tall, cylindrical hair cell (H₂) has several small terminal boutons (N₂) around its base. S² supporting cell. (X 2500)

The striated muscle sections were used for checking the reliability of the histochemical method. They all showed precipitations along the motor nerve fibers and in the neuromuscular endplates (Fig. 8). Specimens which were not incubated with specific substrate did not contain any precipitate. The Prostigmin solution used in the given concentration appeared to inhibit adequately the subneural staining.

COMMENT

Variable densities of copper-sulphide precipitate is demonstrated within the vestibular end-organs of the cat and guinea pig with the

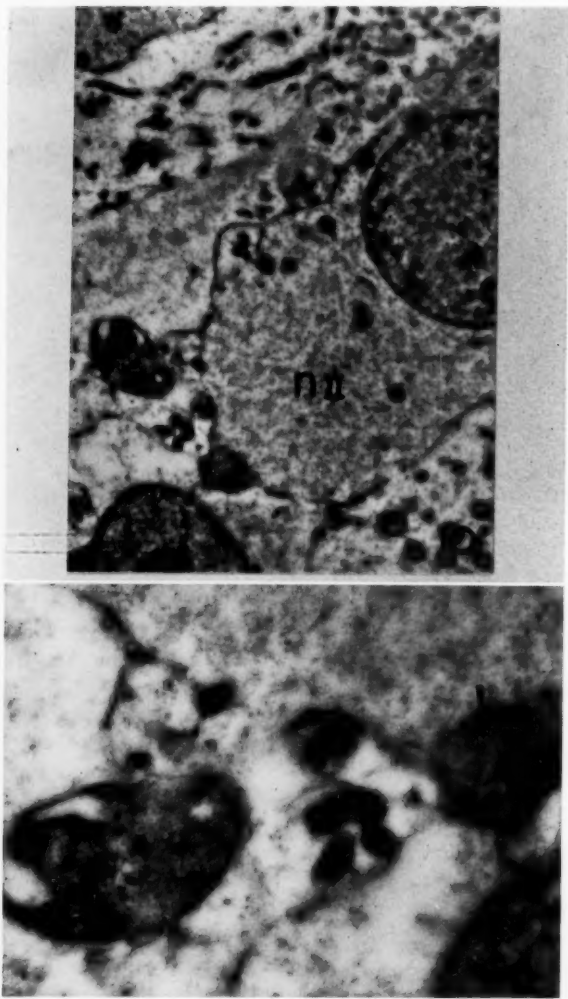


Fig. 10.—Electron-micrograph, showing the innervation pattern of tall hair cell (H₂). N₂ - nerve-endings of different size and density of granulation. (X 7400)

Fig. 11.—Electron-micrograph. Same as Figure 10 in high magnification. Dark granules in terminal boutons probably represent clusters of acetylcholin molecules. (X 16,000)

Koelle-Friedenwald technique, indicating higher concentration of acetylcholin-esterase, respectively its specific substrate, acetylcholin. This reaction appears to be confined to certain structural elements of the peripheral vestibular receptors, notably to the nerve endings beneath and around the neuro-epithelial cells, to the subepithelial neural apparatus and sometimes to branches of the vestibular nerves themselves, whereas those parts of the membranous vestibular labyrinth which do not contain neural elements, were free of precipitate. This must be related therefore to the mechanism of the peripheral stimulation of the receptors concerned. These fibers seem to be evenly distributed along the hair cells of the cristae and utricular macula. In the specimens where the cochlea was also perfused, the characteristic dark stripe was present along the organ of Corti as described by Schuknecht. The controls with inhibitor and some with butyl thiocholine did not show significant reaction, so the reacting substrate is very likely acetylcholine and not some nonspecific choline or thiocholine.

Our experiments definitely confirm the evidence presented, first by Dohlman,³ that there exists in the vestibular cristae and utricle a system of nerve fibers and endings which show relatively large amounts of acetylcholine. While this substance seems to be a necessary constituent of various types of neural elements, analysis of the acetylcholine content of nerve fibers reveals much higher quantities of it in cholinergic than in sensory or afferent neurons. It is generally agreed upon that high concentration of acetylcholine indicates the presence of a cholinergic mechanism. It seems therefore probable that the nonauditory end-organs possess two types of innervation.

The probability of double innervation of the peripheral vestibular receptors has been brought out by recent electron-microscopic studies of Engström,⁵ Wersäll,⁶ and Smith.⁷ The basic structural pattern of these end-organs clearly reveals the dual character of the vestibular sensory hair cells and their nerve-endings (Fig. 9). The short, flask-shaped hair cell (Type 1) is supplied with a large chalice-like nerve-ending, whereas the synaptic regions of the tall, cylindrical (Type 2) neuro-epithelial cells show nerve-endings of different size and granulation (Fig. 10). It is even assumed that the dark granules dispersed richly in some of these small nerve-endings actually represent quantal amounts of the transmitter substance itself (Fig. 11). This difference

in principle between the innervating characteristics of the two types of vestibular sensory cells may be of functional significance.

More information about the cholinergic mechanism, evidently present in the vestibular peripheral receptors, is supplied by the comparison of the operated and nonoperated labyrinths of the same animals. When the whole vestibular nerve was sectioned and the Wallerian-degeneration was allowed to take its course, the acetylcholin esterase activity in the end-organs disappeared although the peripheral ganglia and neuro-epithelial cells did not show signs of degeneration, their blood supply being left intact. It is therefore concluded that the vestibular cholinergic mechanism is efferent.

Neither the central origin and peripheral pathways of the vestibular efferent innervation nor its exact function are known yet, but, if it is permissible to argue from analogy, there is reason in the suggestion that this function is inhibitory. In the cochlea phylogenetically very closely related to the vestibular end-organ, a similar, efferent cholinergic mechanism is demonstrated by Schuknecht. The stimulation of this inhibits the sound induced action-potentials in the acoustic nerve and thus appears to be a feedback pathway for central impulses.⁸

Electrical recordings of vestibular nerve-impulses during stimulation reveal changes in the resting discharge frequency.^{9,10} Trincker has shown that the potential of the neuro-epithelial cells is changed when the cupula is bent one way or the other.¹¹ Thus the increase and decrease of the vestibular action-potential frequency under stimulation is of peripheral origin. It appears however probable that central impulses exert a similar modulating influence on the state of excitation of the vestibular neuro-epithelial cells, as in the cochlea. Electro-physiological experiments are planned to obtain more information about this problem.

SUMMARY AND CONCLUSIONS

1. Our experiments confirm the existence of a cholinergic innervation of the vestibular cristae and utricle.
2. The efferent nature of the cholinergic mechanism is demonstrated: When the auditory nerve is divided, but the blood-supply

of the labyrinth is not disturbed, the specific enzyme activity disappears from the otherwise intact peripheral vestibular receptors.

3. Some electron-micrographs are shown emphasizing the morphological probability for the dual character of the vestibular innervation pattern.

4. It is suggested that the vestibular efferent innervation is inhibitory.

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XL

INNERVATION PATTERN OF THE COCHLEA

THE INTERNAL HAIR CELL

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There have been several electron microscopic studies on the innervation of external hair cells in the guinea pig. Engström¹ and Spoendlin² have described two types of nerve endings. Recent studies by Smith and Sjöstrand³ have confirmed these observations and revealed the presence of other kinds of nerve endings. Observations on the cat⁴ and the rat⁵ indicate that the nerve terminals in the external hair cells in all three animals may be similar.

Less information is available about the internal hair cell. The area between hair cell and habenula perforata with its profusion of nerve fibers is not readily analyzed. In an earlier study in 1957⁶ we found the nerve endings on the internal hair cell were scattered over a larger area and without the polar localization of mitochondria found in the large endings on the external hair cell. Some of the nerve fibers were found to contain more vesicles and we believed these to be terminal fibers destined for the internal hair cells. Spoendlin's observations in 1957⁷ and 1959² were similar. He also observed vesicle-filled neural structures close to, but not in contact with the hair cells. Both he² and Engström¹ interpreted these as nerve endings and suggested they may be inhibitory in nature.

The present studies were made by means of the electron microscope on serial sections, with plastic reconstructions. The observations

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have clarified some of the details of the nerve endings on the inner hair cells and have revealed an interesting nerve relationship.

METHODS

The cochleas of anesthetized guinea pigs were surgically exposed and the fixative (dichromate buffered 1% osmic acid) injected *in vivo* into the perilymphatic spaces. The animals were decapitated, the cochleas excised and immersed in the cold fixative. After fixation was completed, they were washed in Tyrode's solution and dehydrated in ethanol. Pieces of the membranous labyrinth were dissected away in the 70% alcohol. These were embedded in methacrylate. Serial sections were cut on an LKB Ultratome. After mounting on a formvar film, the sections were stained with uranyl acetate solution. They were examined in RCA EMU3A and 3F microscopes at original magnifications of 3000 to 23,000 times, and photographically enlarged at two times or larger. The details of the methods are given in previous publications.^{3,6}

The studies were made on four cochleas from three animals. Seven series were studied which varied in length from 16 to 44 sections. In five of these, every section was photographed. Other series, shorter in length, were examined. Hair cells from the first, second, third and fourth turns were studied. Four different series were cut from one hair cell in the third turn, so that this particular cell was almost completely sectioned.

Reconstructions were made on plastic sheets according to Sjöstrand's technique.⁸ Three reconstructions were made of the nerve endings about the hair cells. Others were made of neural structures in particular areas below the hair cells.

FINDINGS

The internal hair cell is a long cell with a slightly enlarged basal part. The nucleus is centrally placed, and may even be in the upper half of the cell. Medially (toward the internal spiral sulcus) and below, it is covered by the phalangeal cells. Laterally it rests on the pillar cell or a phalangeal cell. A small area on its lateral upper aspect does not appear to be covered by any cell process.

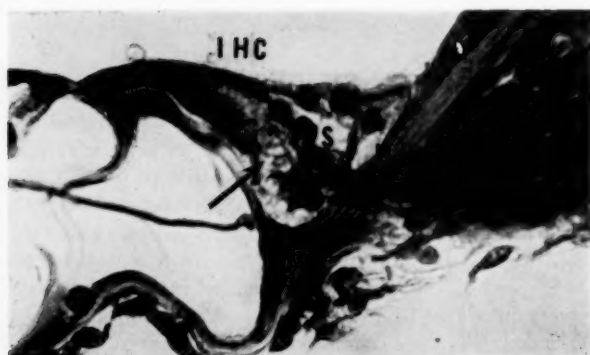


Fig. 1.—Internal hair cell. Protargol stain. 700x.

Some of the nerve fibers may be visualized by examining silver stained material. Figure 1 shows the internal hair cells (IHC) from a paraffin embedded cochlea stained by a modified protargol technique. The nerve fibers penetrate the habenula perforata (HP) of the basilar membrane where they lose their myelin and Schwann cell sheaths. Rounded bundles of spiral fibers (S) are seen immediately above. Radial fibers (arrow) are also visible reaching upward toward the hair cell base. The large number of nerves packed together in tight bundles makes it difficult to distinguish or trace separate fibers.

Figure 2 is an electron micrograph showing the habenula perforata and basal portion of an internal hair cell (IHC) from the third cochlear turn. The bases of the tunnel rod (TR) at the right and phalangeal cell (P) at the left make a funnel-shaped compartment for the nerve fibers. The nerve fibers (N) piercing the basilar membrane are longitudinally sectioned. Their positions suggest that some are destined for the tunnel, others for the internal hair cell and others for the spiral bundles (S). One at the right takes a short direct course to the hair cell base.

Several spiral bundles are visible, some not too well defined. At the extreme right is a large bundle situated between tunnel rod and phalangeal cell. Above it is a very small group. At the left is an-

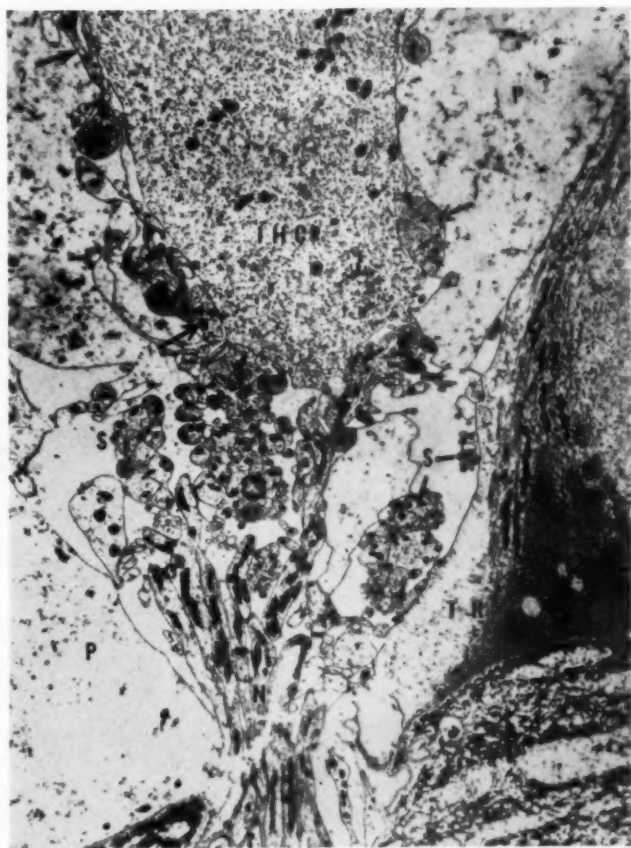


Fig. 2.—Electron micrograph of internal hair cell and nerve fibers. 8,300 x.

other bundle separated by a cell process from the central group. Centrally, a large group of fibers is visible. Only some of these are spiral fibers. Even at this low magnification, it is apparent that some fibers, especially close to the hair cell, are more heavily granulated than others.

A large number of nerves are seen in proximity to the hair cell, at the base or at the sides. Some do not quite touch it. Others are separated from it by phalangeal cell processes. Three nerve endings (arrows) are present.

I. NERVE FIBERS AT THE HABENULA PERFORATA

Figure 3 shows several fibers in longitudinal section passing through the habenula perforata. Remnants of the Schwann cell sheath (S) are visible at the lower margin. The fiber second from the right is smaller than the others, being 0.2 micron in diameter. The diameters of those on either side are 0.5 and 0.7 micron. The small fiber enlarges above, but this may be only a localized dilatation. Parts of three other nerves are visible at the left.

The plasma membrane of each appears as a single membrane. No sheath of any kind is present. The neuropil contains mitochondria, a fibrillar material and a few vesicular structures. Some osmiophilic bodies are also present. The enlargement on the small fiber at center top shows a group of small vesicles.

II. THE SPIRAL TRACTS

Figure 4 shows a spiral bundle of nerve fibers close to the tunnel rod, but separated from it by a phalangeal cell process (P). The bundle is partially enclosed by the phalangeal cells as is often the case. It contains 43 to 55 nerves depending upon where the arbitrary limits of the bundle are placed. The diameters of all the nerves in this bundle were measured. Forty-seven fibers had diameters between 0.08 and 0.3 micron. The remaining eight measured between 0.39 and 0.71 micron. This, then, is a bundle with many small nerves and a few large ones, undoubtedly corresponding to Lorente's¹¹ inner spiral bundle. Obviously the measurements are only estimates because the majority of fibers are not perfectly round but oval or irregular in shape. This may be compression or embedding artifact.

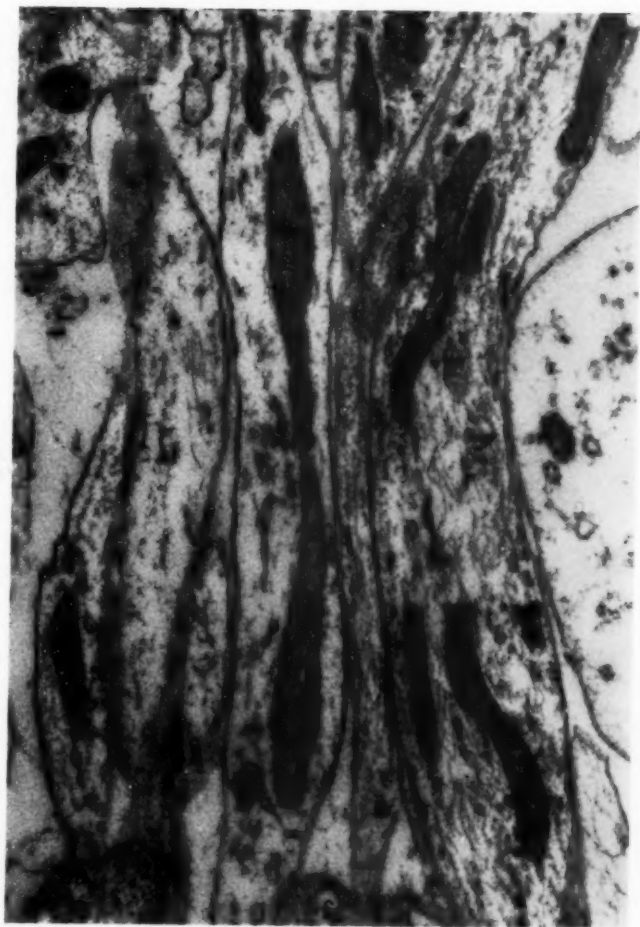


Fig. 3.—Electron micrograph of nerve fibers in the habenula. 27,300 x.

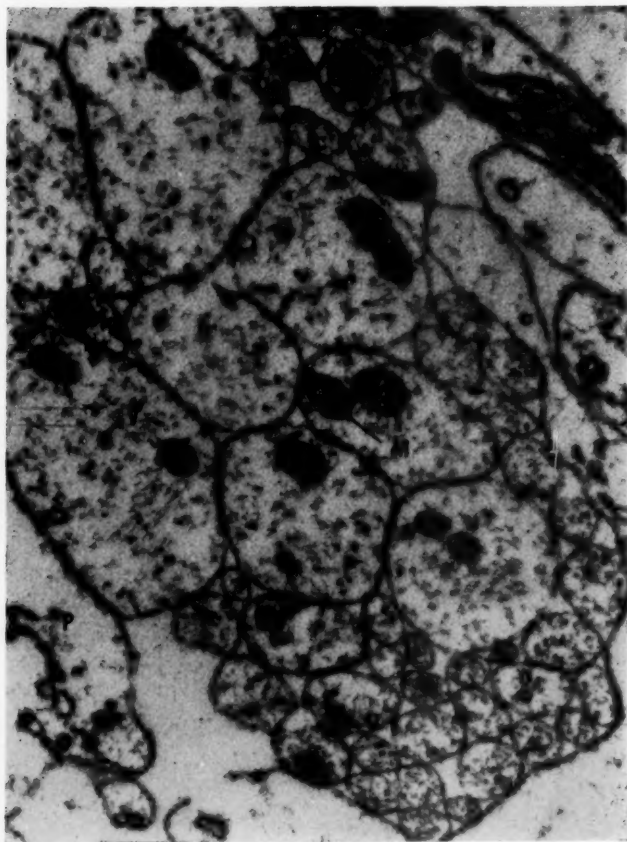


Fig. 4.—Electron micrograph of spiral bundle beneath inner hair cell.
44,000 x.

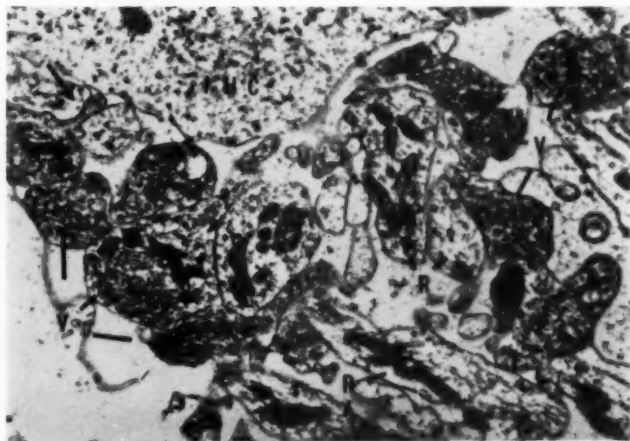


Fig. 5.—Electron micrograph of nerve fibers under inner hair cell. 15,300 x.

All the fibers exhibit similar cytoplasmic details. The plasma membrane is clearly defined with no sheath or other interposed cell processes between adjacent nerves. The cytoplasm shows mitochondria (M) and a fibrillar material. A few vesicles (V) of medium size are often present. The structure of the radial nerve (R) crossing the upper right corner is similar. The radial nerves and the larger spiral fibers are very similar in size and cytoplasmic content.

III. NERVE FIBERS BENEATH THE HAIR CELL

a. *The Radial Fibers.* Figure 5 shows many nerve fibers just beneath an internal hair cell. Some of these are less osmiophilic than others. They are the radial fibers (R). They may also be seen in Figures 8 and 10. These nerves may course in the internal spiral bundle for a short distance or proceed directly from habenula to hair cell. Their cytoplasmic structure changes little in this course. They are similar to the nerves in Figure 3, described above. They lose a little fibrillar material and gain some vesicles, but the change is not remarkable.



Fig. 6.—Electron micrograph of vesiculated nerves close to inner hair cell. 43,200 x.

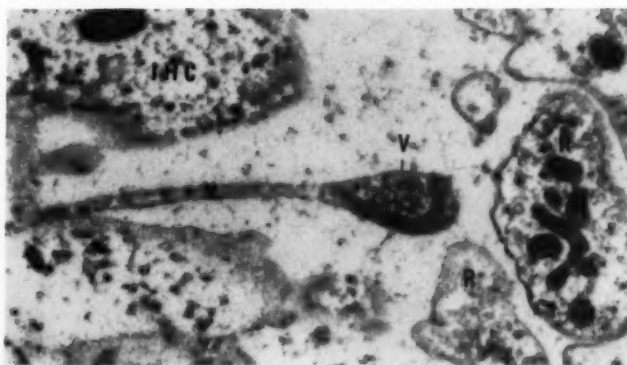


Fig. 7.—Electron micrograph of nerve of fine caliber with enlargement. 20,200 x.

b. *The Vesiculated Nerves.* The other neural structures (V) seen at this level are more dense and highly irregular in shape and size. In Figure 5 they are visible as slender rods, irregularly rounded, oval or rectangular structures. One, at the extreme left (arrow) exhibits a pseudopodium-like extension. At higher magnification (Fig. 6) it becomes apparent that their osmiophilia is due to the presence of large numbers of vesicles. Figure 6 shows the nerves at the left in Figure 5, but three sections removed. The large nerve at right was not identifiable, but it is probably a short radial nerve in cross-section. It shows a group of vesicles (V), mitochondria (M) and a fibrillar or granular material. The four other nerves about it show mitochondria and many more vesicles. The vesicles are distributed throughout the cytoplasm. They vary in size. Generally, the smaller vesicles, which are approximately 250 Å in diameter have centers of low density. Frequently larger granules (approximately 500 Å in diameter) of high density are present, as well as other membrane structures (Fig. 12).

The series and reconstructions have demonstrated that these are enlargements or varicosities on nerves of small caliber. In their course, they are closely related to the radial fibers, sometimes the spiral fibers, and they sometimes touch the hair cell. Figure 7 shows

a small nerve fiber (N) approximately 0.1 micron in diameter, with an enlargement (V) approximately 0.5 micron in diameter at one end. It crosses just below the base of a hair cell. In subsequent sections, the enlargement touched the lower of the two radial (R) nerve fibers and showed a thickened synaptic membrane.

Another small nerve enlargement is shown in Figure 8. Two large vesicular structures (V) are seen at center. A radial nerve (R), light in density, notches the one at right. It divides and partly encloses the radial nerve. In subsequent sections the radial nerve crossed and was slightly embedded in the vesiculated nerve. The structure at left is triangular in shape, and the small nerve stem is indicated at the "q's." The reconstruction revealed the latter to be 1.5 microns long and 0.15 micron in diameter. Its lower end was connected to the nerve at "x." This lower structure may be another enlargement or a nerve of intermediate caliber of which the small nerve is a branch. Undoubtedly, most of the vesiculated structures are varicosities on small nerves, but it is possible that some may belong to nerves of intermediate caliber. The nerve stems as well as the enlargements contain vesicles (Figs. 7 and 8).

These enlargements exhibit considerable variety in size and shape. They may have several processes which, as they curl about and closely follow other nerves, assume grotesque shapes. Some are visible in Figure 5. Others are simple rounded enlargements.

The characteristic close relationship that the varicosities exhibit with the radial nerve fibers and their endings is visible in Figure 5. The vesicular nerves take a general direction which is perpendicular to the radial nerves. Where they approximate the latter, the vesiculated enlargements wind about or partially encircle them. In Figure 10 two rounded vesicular (V) structures are seen on either side of a radial fiber (R) which terminates on the hair cell above. The reconstruction showed that they were two separate enlargements of different small nerve fibers and that both partly encircled the radial nerve. In Figure 2, vesiculated nerves wind about two less dense nerves beside the hair cell (above the arrow). In Figures 11 and 12 three vesicular enlargements lie in close contact with a radial nerve ending.

At places where the vesicular and radial fibers are in contact, the contiguous plasma membranes sometimes exhibit thickenings such as

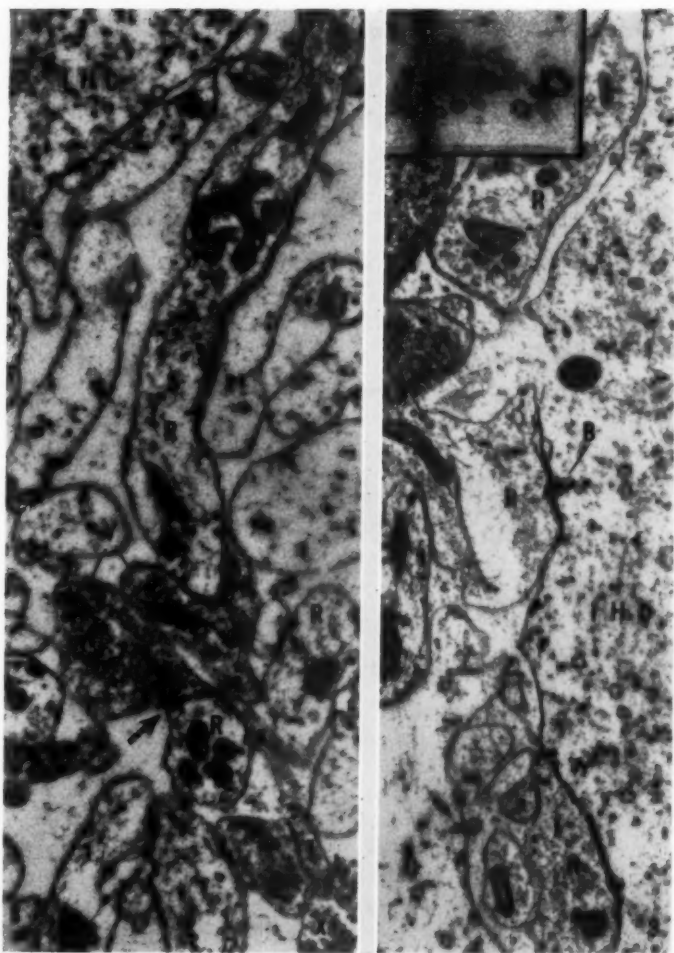


Fig. 8.—Vesicular enlargements, closely related to the radial nerves. 24,000 x.

Fig. 9.—Three radial nerve endings; a synaptic bar at center, enlarged at inset. 20,000 x. Inset, 68,000 x.

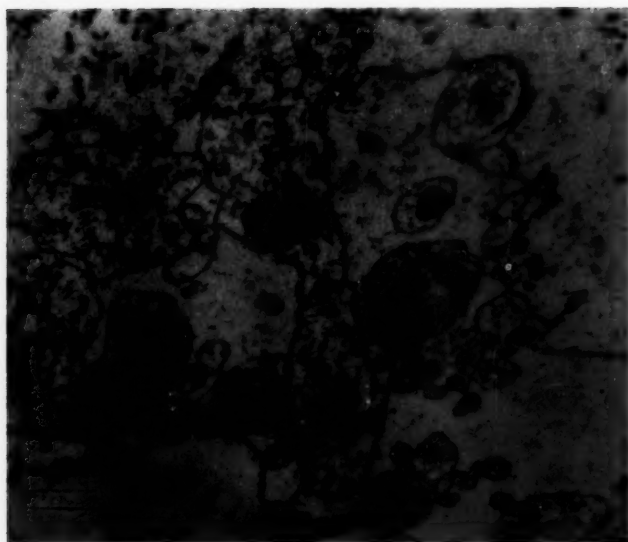


Fig. 10.—Vesicular enlargements around the radial nerves. 20,400 x.

are described at the radial nerve ending-hair cell synapse, and at synapses elsewhere.⁹ These are illustrated in Figures 6 and 8 (arrows).

The osmiophilic layers of the contiguous nerve plasma membranes in Figures 6 and 12 are separated by a fairly constant narrow light interspace approximately 115 \AA in width. The two membranes, however, are not precisely parallel. Occasionally, and over only a short distance, the two membranes may become more parallel and seem to be thickened. This is visible between the arrows in Figure 6. Here, the lighter space between the two osmiophilic layers is approximately 190 \AA in width and appears to contain some dark material. Inside both nerve fibers also, a dark material is visible. This seems to be attached to the plasma membrane and frays out into the cytoplasm. There does not appear to be a change in the thickness of the osmiophilic layers, but rather in the attached material.

No evidence for a network of these nerves has been found. This does not preclude the possibility of such a pattern. It could be that

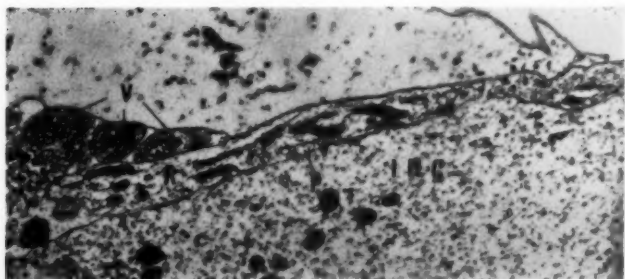


Fig. 11.—Long radial nerve ending, ascending side of hair cell. 9,900 x.

none of the series was long enough to demonstrate that type of pattern.

NERVE ENDINGS

The nerve endings are of two kinds: 1) long, and 2) rounded.

1. The long endings are the terminals of the radial fibers. Most of these approach the hair cell from below, coming either directly from the habenula or from the spiral tracts. They touch the hair cell at the base and take a longitudinal course upward. Figure 11 shows a long nerve ending (R) with several vesiculated nerves (V) adjacent to its outer surface. This ending was almost 9 microns in length. Others, particularly those terminating at the base, are shorter.

In their course along the hair cell, the nerves are not always in close contact with the sensory cell plasma membrane. Rather, they seem to touch it only in places. Fairly wide spaces separating the two plasma membranes may be seen in Figures 9, 11 and 12. Sometimes a phalangeal cell process (P) is interposed (Fig. 11). However, even when no extraneous cell is interposed, the synapse shows further differentiation. Figure 12 shows the long nerve ending (R) in Figure 11 at higher magnification. Between the arrows the synaptic membranes of nerve and hair cell are in close apposition. The osmiophilic layers of the plasma membranes are smooth, parallel and more dense than outside the arrows, with the neural membrane being slightly

the thicker. They are separated by a space approximately 145 Å wide. On either side the membranes diverge with a consequent widening and irregularity of the light space between. Figure 9 shows three different nerve endings (R). The lower and central one show the synaptic membranes to be thickened only in part. The upper nerve exhibits no thickening.

A synaptic bar (B) is visible in Figure 9 and also in Figure 2 adjacent to the ending at lower left. The synaptic bar is a flat, plate-like osmiophilic structure surrounded by a single row of vesicles. It is found in the hair cell cytoplasm adjacent to some synapses, and has been described, as found in both internal and external hair cells in a previous publication.¹⁰ In the internal hair cell, it has been found only adjacent to the long nerve endings, and only in places where the synaptic membrane shows the greater density and thickening. It is not possible to determine if it is always present at the thickened synaptic membranes, because all endings could not be completely followed, but it was never observed adjacent to the synaptic membranes of low density. One of these structures is shown in the inset at higher magnification.

The structure of the long endings is only slightly different from their nerves below the hair cell. They show a paucity of formed elements. The ending in Figure 12 shows mitochondria (M), vesicles of variable size and a little fibrillar material. The fibrillar material disappears and more vesicles are found as the nerves approach their terminals. The amount of vesicles varies, and some approaching nerves and endings contain a fair number.

2. The other kind of ending is small, rounded and contains many vesicles. One is visible in Figure 12 at lower right (SV). It is slightly oblong, approximately 0.4 micron in its shortest diameter. It contains mitochondria, vesicles and some granular material. It is very similar in structure to the vesiculated varicosities at the left. Another is shown in Figure 13. It contains many vesicles. The large light vesicle near the tip may be artefact. The synaptic membrane of neither of these two endings shows any thickening. No synaptic rod has ever been observed adjacent to them. The contrast between cytoplasmic structure and nature of the synapse in long and round endings is well marked in Figures 12 and 13.

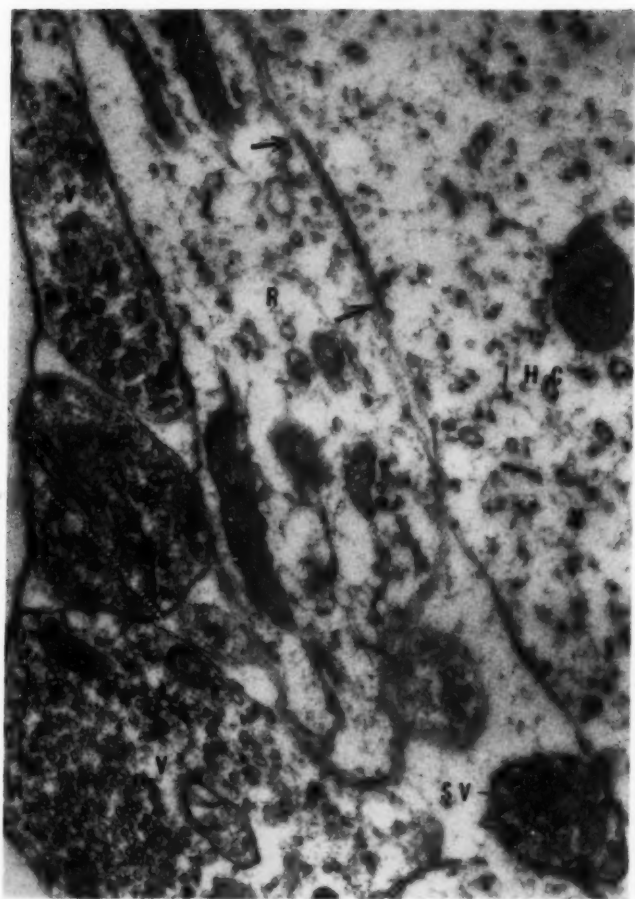


Fig. 12.—Long and small round nerve endings; three vesicular enlargements at left. 44,000 x.

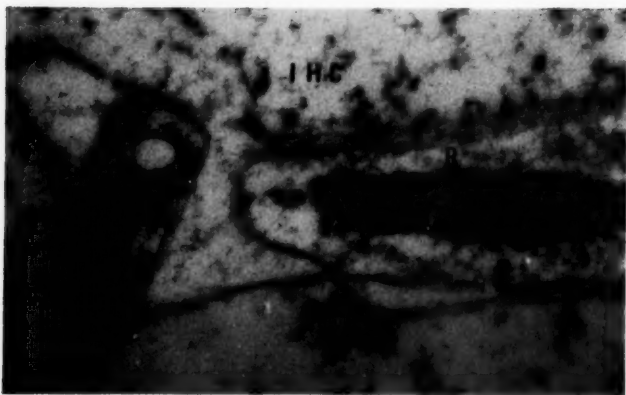


Fig. 13.—A small, and part of a long ending on inner hair cell. 48,000 x.

The term "ending" is used advisedly in describing these synaptic structures, because it could not be determined whether they are actually terminations. It has been observed that some of the vesiculated nerves and their varicosities touch the hair cell and then withdraw and continue elsewhere. The pseudopodium (arrow) in Figure 5 illustrates this. The endings shown in Figures 12 and 13 belong to the vesiculated nerves, but the series were not long enough to determine if they ended at the hair cell.

It seems certain that most of these rounded endings belong to the vesiculated nerves, but how many, if any, actually terminate at the hair cell could not be determined.

RELATION OF PHALANGEAL CELLS TO THE HAIR CELLS

The inner phalangeal cells show a relationship to the inner hair cells that is not duplicated external to the tunnel. In Figures 2 and 5 processes of the phalangeal cells can be seen in between the nerve endings and near the hair cell. It can be observed that the hair cell membrane is not precisely round in contour but has projections or spines. Figure 14 shows that slender cell processes (arrows) actually invaginate into corresponding indentations in the hair cell membrane.

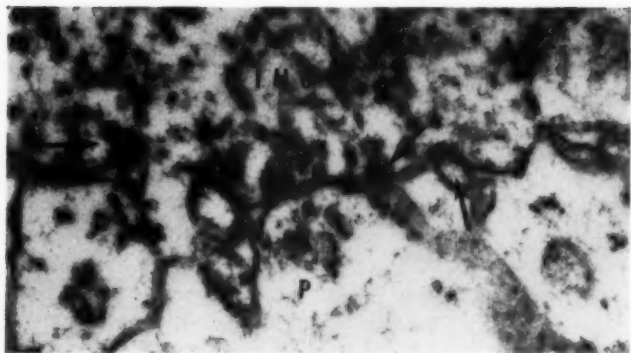


Fig. 14.—Several processes of the phalangeal cell invaginating into hair cell membrane. 48,000 x.

The process at the left is clearly a part of the phalangeal cell (P). Many of these invaginating processes can be found, more often about the base of the cell. Some are rather deeply embedded in the hair cell cytoplasm, sometimes to a depth of 0.2 micron. The serial sections have shown that the processes actually do belong to the phalangeal cells. The nerves sometimes exhibit irregular protuberances near the hair cell but none have been found to actually invaginate into the inner hair cell. Processes of the sensory cell are sometimes likewise embedded in the phalangeal cells.

COMMENT

Two features stand out clearly concerning innervation of the internal hair cell: 1) The radial nerves terminate at the base and ascend the sides of the hair cell where the endings may reach a considerable length. 2) Other nerves, characterized by enlargements filled with vesicles and mitochondria wind among the radial nerves and are adjacent to their endings. At least some of these touch the hair cell briefly.

The large radial fibers are not too difficult to visualize with silver stains. There seems little doubt these are the nerves described

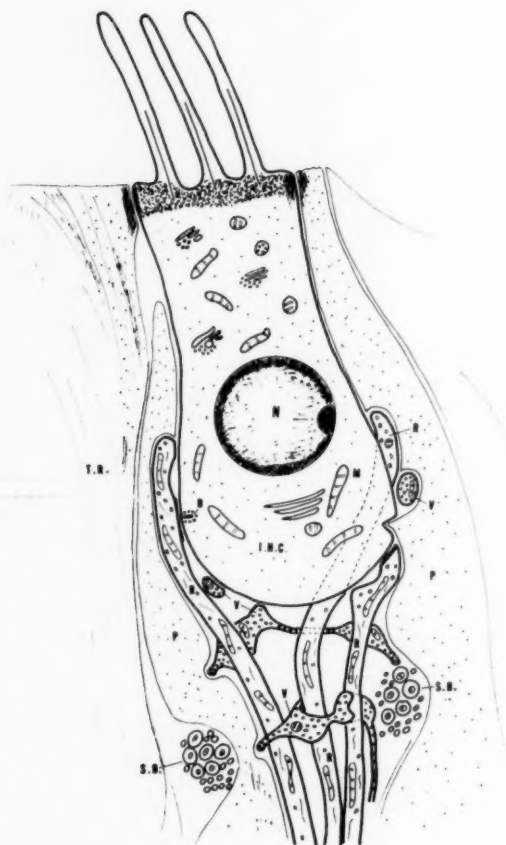


Fig. 15.—Schematic drawing showing innervation of the internal hair cell of the guinea pig cochlea. B, synaptic bar; IHC, internal hair cell; M, mitochondrion; N, nucleus; P, phalangeal cell; R, radial nerve fiber; SB, spiral nerve bundle; TR, tunnel rod; V, vesiculated nerve with enlargement.

as radial fibers, terminals of the spiral ganglion cells, by Lorente de No¹¹ and Fernandez¹² among others. Some can be seen to go almost directly to the hair cell. Others deviate toward the spiral bundles. The presence of large fibers in the spiral bundles medial to the hair cell leads to the assumption that some of these travel in a spiral direction for a variable distance before terminating.

Their terminals which appear as long fibers extending sometimes halfway up the cell have been observed by histologists utilizing silver stains. Cajal¹³ very clearly illustrated the long terminals, in all respects similar to the observations here. Their internal structure is similar to that of some other dendrites, especially in the Pacinian corpuscle¹⁴ and the vestibular nerves.^{15,16} The nerve endings in Meissner's corpuscle exhibit more mitochondria.¹⁷ Even though these nerves may ascend the hair cell for a considerable distance, they are not necessarily in synaptic contact for the entire extent. Phalangeal cell processes are interposed in some places, and the membrane thickenings, with associated synaptic bar, are limited in extent. The micrographs may be interpreted in either of two ways. The thickened membrane may be present as a very narrow band along the greater part of the ending, or it may be confined to a small membrane segment. Longer series and further observations are necessary to elucidate this point. It is possible that although all of the closely apposed neural-sensory cell membrane possesses synaptic potentialities, the entire ending is not simultaneously active. The synaptic bar and thickened membrane may be indications of localized activity. The concept that nerve endings are dynamic structures is not new and has been advanced by others.^{9,18}

The configuration and relations of the large vesicular structures were not previously recognized, and in all probability they are the elements mostly responsible for the aura of confusion existing about this area. Lorente de No¹¹ described a spiral plexus of fine fibers beneath the inner hair cell. The Portmanns¹⁹ also described fibers of fine caliber wandering among the radial fibers in a spiral direction which they were able to differentiate by means of the Weber stain. They believed these to be the efferent fibers. It seems probable that the vesiculated nerves are branches of the fine fibers in the spiral bundles and that both Lorente de No's and the Portmanns' descriptions correspond at least in part to these. Engström and Wersäll also described small fibers with granules in the inner spiral bundles.²⁸

Nerve varicosities similar to these have been described by Hess²⁰ in the ganglia of the cockroach. Insect nerve fibers frequently end on other nerves and he interpreted them as nerve terminals. Beaded axons of nerves ending in epithelium have been repeatedly described after methylene blue and silver staining, but it is not known if they correspond to the kind of varicose structure described here. Zander and Weddell²¹ described numerous beaded fibers in the corneal epithelium. Whitear,²² utilizing electron microscopy, found some mitochondria-filled varicosities on these nerves and believed them to be confirmatory of Zander and Weddell's findings. Garven and Gairns²³ have suggested that the beads they described on terminal sympathetic fibers might represent release points for humoral substances.

These vesiculated structures have all the characteristics usually associated with synapses: mitochondria, numerous small vesicles and thickened plasma membranes at point of contact. The membrane thickenings are particularly found adjacent to the radial nerve fibers, either below the hair cell or on their endings. It seems apparent that a single fiber may make synaptic contact, by means of its enlargements, with several radial fibers and perhaps hair cell before terminating. All the structural evidence supports the concept that these are effector synapses on the afferent nerves. Two possibilities seem open in regards to their identity. They may be of parasympathetic or sympathetic origin. It is not known that any of the former travel with the VIII nerve in the modiolus. Investigators utilizing silver stains,^{11,24} have not been able to demonstrate any sympathetic fibers accompanying blood vessels peripheral to the modiolus. This possibility then seems remote. The alternative is that they may be terminals for the efferent olivo-cochlear bundle described by Rasmussen.²⁵ The vesiculated structures originate from fibers of small caliber, which corresponds to descriptions of the fibers in the efferent tract.^{19,26} The present observations have shown only two kinds of terminal fibers, morphologically differentiated, below the inner hair cell, i.e., the afferent radial nerves, and these vesiculated nerves. The location of their synaptic bulbs on the afferent dendrites would fit in well with Galambos' evidence²⁷ that the stimulation of the olivo-cochlear bundle inhibited activity of the cochlear nerve. There seems little doubt that these are terminal fibers of Rasmussen's efferent tract.

Enlargements containing mitochondria and vesicles are also found on the nerves beneath the external hair cells.³ They are not as numer-

ous, neither do they exhibit the almost syncytial nature of those described here. They are similar in that they are closely related to neighboring nerves. They are most often found in between the rows of sensory cells, an area which was not within the scope of our previous studies, and has not been given attention by others so that the information is sparse. The Type 2A endings found on the Type B external hair cells³ present a close structural similarity to the varicose nerves at the inner hair cells. They only touch the hair cell, but are in extensive contact with other nerve endings and nerve fibers. If the proposal that the vesicular fibers represent the olivo-cochlear bundle internal to the tunnel is correct, then the efferent tract could be represented by the varicose fibers³ and perhaps the Type 2A endings, external to the tunnel.

The comparison between innervation of internal and external hair cells may be extended to other endings. One long ending, similar to the radial fibers was observed on one external hair cell in the previous study,³ but such endings are infrequent there. The small Type 1 endings on the external hair cells are similar in structure to the radial nerves, except that they do not exhibit membrane thickenings. Both, and only these endings, exhibit the synaptic bar. Added support is thus given to the belief that the Type 1 endings are the regular afferents on the external hair cells. No nerve endings have been found on the inner hair cell comparable in structure to the large Type 2 endings¹⁻³ found in large numbers on the Type A external hair cell. Neither is there found an accessory synaptic membrane in the inner sensory cell adjacent to any of the endings. The Type 2 endings seem to be unique on the external hair cell.

SUMMARY

1. The inner hair cell in the guinea pig cochlea exhibits two kinds of nerve endings:

a) Long endings, which are the terminals of the radial nerves. These may reach considerable length as they ascend the sides of the hair cell. Their cytoplasm shows mitochondria and a few vesicles.

b) Smaller, rounded endings with many vesicles. Some of these have been traced to nerves of small caliber.

2. Two kinds of nerve fibers can be differentiated beneath the inner hair cell:

a) The nerves of large caliber which are the radial nerves destined for the sensory cell.

b) Nerves of small caliber which exhibit enlargements filled with vesicles and mitochondria. They wind among the radial nerves and apparently are in synaptic contact with them. They sometimes also touch the hair cell. Their actual terminals could not be determined.

3. It is proposed that these nerves of small caliber with the vesiculated enlargements may be identical with Rasmussen's efferent bundle.

EUCLID AVE. AND KINGSHIGHWAY

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XLI

PRESSURES OF THE LABYRINTHINE FLUIDS. II.

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AND

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Anson and Bast¹ have stated that the total volume of the bony labyrinth equals 0.2 ml and that this space must contain all labyrinthine cellular structures and all fluids, including both perilymph and endolymph. The technical difficulty of securing pressure determinations of labyrinthine fluids is evident. In 1948 Weille et al.² reported pressuregrams of both endolymph and perilymph and were surprised to note that the pressure of perilymph appeared greater than that of endolymph.

In pressure there are hydrostatic and osmotic components. To understand the contribution of the osmotic pressure, one must know either the total milliosmolar pattern or the exact chemical composition of both endolymph and perilymph. Changes in the chemical composition of these fluids may be important in certain cases of labyrinthine deafness, tinnitus, and vertigo. Lindsay³ has speculated that one cause of nerve-cell degeneration in cochlear deafness may be related to alterations in labyrinthine fluid pressure and the chemical composition of the labyrinthine fluids.

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Even though perilymph and endolymph are minute in quantity, they are extracellular fluids and must be considered in total body fluid balance. Bland⁴ estimated that about 60 per cent of body weight is water and that roughly 75 per cent of this is within cells with about 25 per cent as plasma, lymph and fluids between cells (extracellular fluid). It must be emphasized that the small volume of perilymph and endolymph does not prohibit their sharing in the physiological and pathological changes common to other extracellular fluids.

The experiments of Weille et al.² were not conclusive, but they were of sufficient interest to encourage additional experiments.

METHODS

The guinea pig was the experimental animal. Sodium pentobarbital was used for anesthesia; the initial intraperitoneal dose was 40-45 mg per kilogram of body weight. Additional doses sufficient to maintain deep anesthesia were given as required throughout the experiment. Most guinea pigs received a constant supply of moistened oxygen via an intratracheal cannula to suppress respiratory movements. This method has been described in detail by Irwin and Macdonald.⁵

An incision was made from the midventral line of the neck to the mandible just above the area where the anterior and posterior facial veins approach the masseter muscle. Careful dissection separated the sheath of the external jugular vein from the masseter muscle. The tissue and blood vessels were pushed to the medial side of the masseter muscle; then the mandible was fractured. A retractor was used to clear the area between the mandible and soft tissues of the neck. The exposed sternocleidomastoid muscle was severed. The posterior belly of the digastric muscle was removed, and by a blunt dissection the bulla cell was brought into view to be opened with a small rongeur in order to expose the cochlea.

With the aid of the Zeiss operating microscope (10X-40X), fenestrae were made. A band of pigmented cells marks the area of the stria vascularis on all turns of the cochlea. When pressures of endolymph were to be secured, fenestrae were made within the pigmented cell area. If the pressure of perilymph was desired, a fenestra

was made just above or below the pigmented area. All fenestrae had a diameter of 30-50 micra. A small hand instrument with a Dixon pivot drill (.003 inch) was used to make the fenestrae.

When pressures of perilymph were to be measured through the round window, an endaural surgical approach, as described by Weille et al.,² was used.

A capacitance electromanometer was used to measure pressure. This instrument and recording equipment were described by Rappaport et al.⁶ A plastic adapter connected the microcannula to the microphone. The microcannulae were made from quartz or pyrex tubing 1-3 mm O.D. with T 5/20 female joint. The tip of the microcannula was about 75 micra in length and had an internal diameter of 20-30 micra. The microphone, adapter, and microcannula were filled with Ringer's solution. It was important to exclude air bubbles from the system and to fill the microcannula to its very tip.

When it was desired to measure the pressure and DC potential simultaneously, the system was changed. A glass adapter with an Ag-AgCl electrode was designed to fit between the plastic adapter and the microcannula. The microcannula and adapter were filled with 0.9% KCl to match the KCl concentration of endolymph. Since the Ag-AgCl electrode cannot be coupled by KCl to the bottom plate of the condenser microphone which is grounded, the microphone was filled by spindle oil or xylol. The adapter was partially filled by spindle oil or xylol and on top of this was layered 0.9% KCl. Figure 1 visualizes this system.

The DC potentials were amplified by a DC front end (Bioelectric Instrument Type D Amplifier) which has an input impedance of 10^9 ohms. The output of this amplifier was connected to a Tektronix High Gain Differential Calibrated DC preamp Type 53/54D plug-in unit, and the potentials were displayed on a Tektronix oscilloscope as well as being recorded on a Grass Model 5A Polygraph. The potentials were recorded differentially to minimize effects of drift in the amplifiers.

The ground electrode was a silver chloride wire placed in KCl soaked cotton on the neck of the guinea pig. The reference electrode, a glass pipette, the diameter of which was about 40 micra, was filled

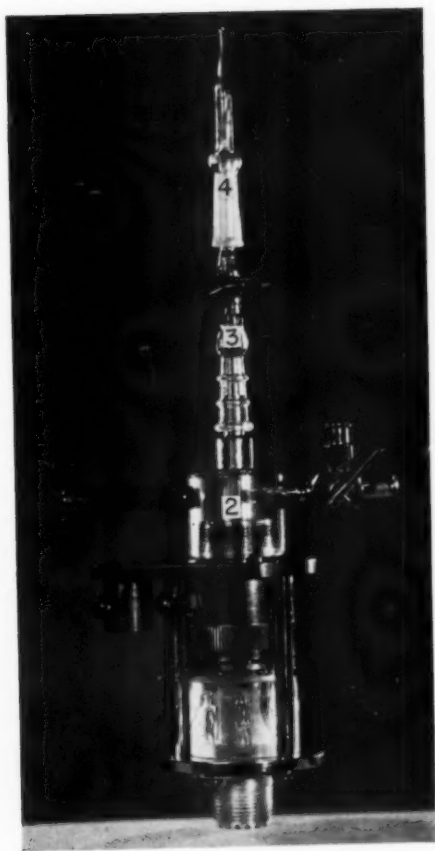


Fig. 1.—Microphone containing transducer.

with 0.9% KCl and was placed on the neck of the experimental animal. The recording electrode was incorporated into the pressure cannula as previously described.

Histological studies were made of the inner ear of many experimental animals to define the area of entry of the microcannula. On occasion the living anesthetized guinea pig was decapitated, and its skull was fixed in 10 per cent formalin solution for 24 hours. Other experimental guinea pigs were perfused through the aorta with filtered Heidenhain-Susa solution. Several days were allowed for decalcification in Decal. Then the temporal bone was dehydrated by running through alcohols, and finally the preparation was embedded in celloidin. Serial sections about 20 micra thick were made with a sledge microtome (Leitz-"Wetzlar") and mounted after being stained with Mayer hematoxylin and water-soluble eosin.

EXPERIMENTS

Experiments can be grouped into five distinct categories:

GROUP 1—In each guinea pig the pressure of endolymph or perilymph was measured.

GROUP 2—The pressure of perilymph or endolymph was obtained. Then sections were prepared to determine whether the microcannula entered the correct scala.

GROUP 3—The pressure of endolymph or perilymph was recorded and simultaneously an attempt was made to secure a DC potential.

GROUP 4—Either the pressure of endolymph or perilymph was secured simultaneously with the attempt to measure the DC potential. Histological sections of the temporal bone were made correlating area of fenestration with pressure and DC potential.

GROUP 5—In the same animal the pressures of endolymph and perilymph were measured. Histological sections were made to determine the areas of entry of the microcannulae.

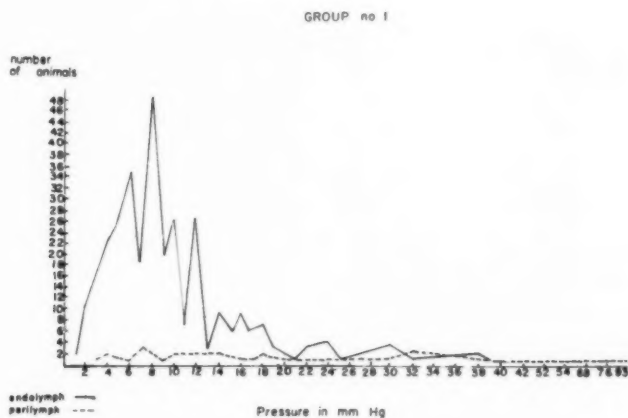


Fig. 2.—Plastic reservoir adapter.

RESULTS

GROUP 1—Attempts to measure pressure of endolymph were made in 342 guinea pigs. The pressure was less than 10 mm Hg in 206, but the pressure was 10 mm or more in 136 animals.

The pressure of perilymph was measured in 37 guinea pigs. Twenty-six of these animals appeared to have a perilymph pressure greater than 10 mm Hg, and 11 showed a pressure of less than 100 Hg.

Figure 2 is a graph of the above data.

GROUP 2—In 59 guinea pigs attempts to measure the pressure of endolymph were followed by histological studies of the cochlea. Thirty-six of these animals had an endolymphatic pressure of less than 10 mm Hg, whereas 23 had an endolymphatic pressure of 10 mm Hg or more. The histology of 36 indicated that the microtip of the pressure cannula had entered the scala media and that in 23 the microtip had entered scala vestibuli or scala tympani. Perilymph pressure-grams were obtained from 34 guinea pigs. Again, histological sections were made of the cochleas. Twenty-five pressures were greater

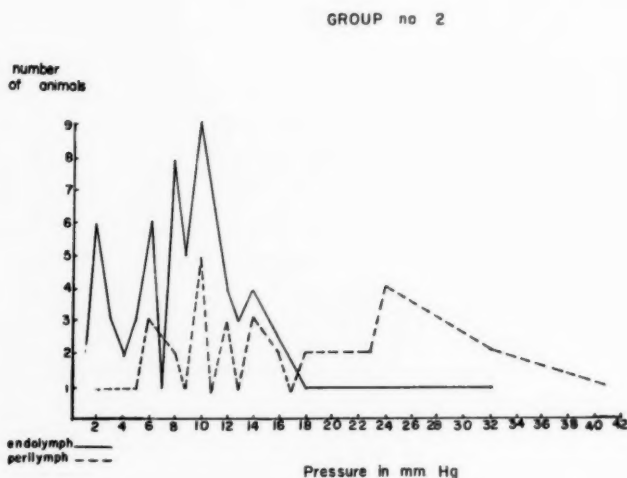


Fig. 3.—Glass adapter with Ag-AgCl electrode.

than 10 mm Hg, and nine were less than 10 mm Hg. The histology of all 34 inferred that the tip of the pressure cannula had entered the scala tympani or the scala vestibuli.

Figure 3 is a graph which incorporates the above data.

GROUP 3—In seven guinea pigs microfenestrae were made over the pigmented area of the second or third turn of the cochlea. In all seven animals an attempt was made to measure the pressure and the DC potential simultaneously. All seven showed a pressure of less than 10 mm Hg. Only in four, however, was an adequate DC potential simultaneously secured.

Five guinea pigs had microfenestrae drilled just above or below the pigmented areas of the second or third turn of the cochlea. Again pressures were secured and attempts to measure DC potential were made. No DC potential was secured in any animal, and in all but one animal the pressure was greater than 10 mm Hg.

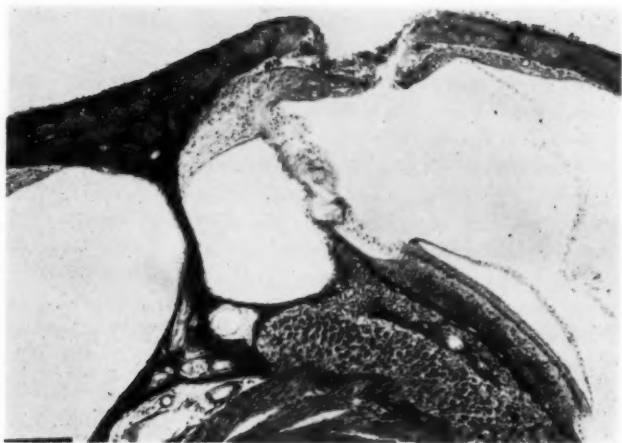


Fig. 4.—Microcannula.

GROUP 4—Attempts to measure pressure of endolymph and DC potential simultaneously were made in twenty-one guinea pigs. After each experiment was concluded, the animal was perfused, and histological sections of the cochlea were made to attempt to determine the area of entry of the microcannulae. No DC potential was recorded in six of these experiments. In these six, histological sections suggested that the tip of the microcannula had entered perilymph rather than endolymph, but in only one of these six did the pressure exceed 10 mm Hg. In fifteen guinea pigs pressure and DC potential were successfully measured simultaneously. All fifteen showed pressures less than 10 mm Hg. Histological sections, however, suggested that the perilymph scalae or both perilymph and endolymph scalae had been entered by the microcannulae in five of these fifteen. In the other ten, histology favored the entry of the microcannula into the scala media only. Figure 4 shows a section from one of these ten.

Nine experiments were made to secure a pressure of perilymph while testing simultaneously for a DC potential. All nine were perfused and histological sections made to determine entry of cannulae. Pressures were secured in all nine, but only six showed pressures over

10 mm Hg. In no animal was a DC potential recorded. Histology indicated that either the scala tympani or scala vestibuli had been entered in all nine.

GROUP 5—There were 18 guinea pigs in which the pressure of endolymph and perilymph were measured, one after the other, with the same cannula or with two separate cannulae. The endolymphatic pressure was always secured from a different turn of the cochlea than perilymphatic pressure. Histological sections of each cochlea were obtained. Pressure of endolymph was always less than pressure of perilymph in each animal. Histological sections which are available indicate that the tip of the pressure cannula entered the scala media when the pressure of endolymph was being secured and into the scala vestibuli or scala tympani when the pressure of perilymph was being measured.

COMMENT

A careful survey of these experimental results clearly shows that much work remains to be done, but there exists the probability that the pressure of perilymph is greater than that of endolymph.

The potential sources of error are many. The microfenestrae were drilled by hand. It was necessary to drill right to the spiral ligament. Frequently experimental animals had to be discarded because of microscopic evidence of leakage of either perilymph or endolymph. Indeed, over sixty per cent of our experimental animals were discarded because of this difficulty. Naturally, there is no guarantee that the accepted animals did not possess leaks not visualized with the aid of the microscope.

The experiments in which pressure measurements and DC potentials were recorded simultaneously required the use of xylol or spindle oil in the system. It was learned that xylol acted on all types of plastic of which the adapters were made. Naturally, a loose adapter could lead to gross errors in pressure measurements. Spindle oil could seep through the microphone and tended to interfere with pressure recordings.

When histology suggested that we were in the scala media, failure to record a DC potential sometimes was noted. Békésy⁷ showed a

positive DC potential in endolymph. In 1959, Tasaki et al.⁸ demonstrated that the positive potential of endolymph was lowered by damage to stria vascularis. Misrahy et al.⁹ in 1958 found that anoxia and damage to stria vascularis resulted in a decreased endocochlear DC potential. These findings would suggest that the DC potential is reliable, and it is possible that in some experiments we damaged the stria vascularis to such an extent that the DC potential was not recorded. Even if the histology indicated that the microcannula entered the scala media, there was always the possibility that the very tip could have been in perilymph. The tip is fine, and it is conceivable that it could pierce Reissner's membrane without damaging it sufficiently to be detected on histological sections.

Another factor of possible error is worth consideration. If the tip of the cannula entered the scala where the pressure was being measured and penetrated deeply, it might, itself, create a certain hydrostatic pressure by volume displacement. This could vary to little or nothing when the penetration of the tip of the tube was slight. It would seem reasonable to assume that with many experiments there would be compensation for this possible error by the variety of positions of placement.

The concept of osmotic pressure offers the temptation to simplify inner-ear fluid physiology, despite the fact that this may be erroneous. Suppose in the attempt to explain the experimental observation made by us that, in general, perilymph pressure is higher than endolymph pressure, we assume that this depends entirely on a difference in osmotic pressure of the two fluid systems. Stuhlman¹⁰ has defined the osmotic pressure of a solution as "the maximum hydrostatic pressure produced when a solution and solvent are separated by a perfect semi-permeable membrane" or "the equivalent of the external pressure which must be applied to a solution in order to prevent the passage of the solvent into it through a perfect semi-permeable membrane." Roberts¹¹ has stated that the crystalloids of the extracellular fluid compartment of the body have a force of about 5,000 mm Hg of osmotic pressure. If perilymph were separated from distilled water by a synthetic membrane permeable only to water, then water would rush through the membrane into the perilymph to dilute it. The same would be the case with the same experiment using endolymph instead of perilymph. In each case the membrane would be impermeable to all substances in solution. If the total concentration of the various

units in the perilymph or endolymph exercising osmolarity changed, then the magnitude of the pressure would be modified accordingly. An easy transposition in theory is to keep this concept in mind, and interpolate a semipermeable membrane between perilymph and endolymph which would permit particles of low mass such as sodium, potassium, calcium, chloride, or carbonate to pass through, but not high mass particles such as protein molecules. In a non-living system one could predict with some assurance what would then occur since each particle in each solution contributes its force not by its size or valence, but by its numbers in concentration; e.g., a protein molecule, a red blood cell, or a potassium ion, a sodium ion, or other particles all are exactly the same from the point of view of exercising osmotic pressure. Therefore, the actual osmotic pressure in this experiment would be the difference in total milliosmoles of the two sides of the membrane, and there would be dilution of the more concentrated solution by passage of water into it with simultaneous loss of particles into the weaker solution.

It is tempting, especially to clinicians, to visualize Reissner's two-cell thick membrane as such a semipermeable system. Unfortunately, we do not know the degree of permeability of Reissner's membrane, or the more complicated basilar membrane and spiral ligament, nor are all of the components of the chemical pattern of endolymph and perilymph quantitatively known. Of utmost importance is the fact that living cells of even the thinnest membranes can contribute energy patterns to alter or reverse mere physiochemical calculations.

Davis¹² is of the opinion that the walls of the membranous labyrinth are practically impermeable to ions, but White, Handler, Smith and Stettin¹³ state that "all cells are freely permeable to water." It would seem that we are justified in concluding tentatively that either perilymph supplies some water to endolymph or that the higher perilymphatic pressure is necessary to prevent leakage of at least water from endolymph into perilymph.

Two further points require consideration. These are: 1) Substances dissolved in water conform exactly to the basic *gas* laws. Thus, in a given quantity of solution the osmotic pressure varies both with the concentration of the solutes and with the absolute temperature. (It is therefore possible to determine the total osmolarity of a

solution by measuring depression of the freezing point without knowing the exact quantitative chemical components in the fluid.) 2) The arteriovenous arcades of the spiral ligament.

These factors make it conceivable that exposure of the guinea pig cochlea to room temperature by opening the bulla might affect the pressure measurements reported. A slight increase or decrease in temperature of the endolymph, for example, would increase or decrease its osmotic pressure definitively. The arteriovenous arcades of the spiral ligament¹⁴ appear to equal the number of arterioles to the capillary networks of the spiral ligament and stria vascularis. The primary function of arteriovenous anastomoses wherever present has been suggested by Krogh¹⁵ to supply heat to the part. Changes in temperature may influence pressures of the labyrinthine fluids by the osmotic pressure response of solutes in conformity with basic gas laws; i.e., the osmotic pressure of a solution varies directly with the absolute temperature (273 plus the centigrade reading). At a body temperature of 37°, the absolute temperature would be 273 plus 37, or 310°. A 0.5 degree centigrade alteration would elevate or depress the osmotic pressure of extracellular fluid by 1/620. If the osmotic pressure of extracellular fluid at 37° C is about 5,000 mm Hg, then a rise of 0.5° C would raise osmotic pressure about 8 mm Hg. If this temperature rise applied equally to perilymph and endolymph, the rise would be uniform and cancel out. But if one fluid were affected more than the other, e.g., endolymph, then an appreciable physiological change would occur. The anatomical location of the arteriovenous arcades in the spiral ligament is almost exactly between the levels of the attachments of the basilar membrane and Reissner's membrane. It is therefore likely that vessels primarily delivering heat to the area will have a greater immediate effect upon temperature alterations of endolymph than of perilymph. This possibility may have clinical implications in certain labyrinthine disorders.

CONCLUSION

Experiments to date suggest that the pressure of perilymph in the living guinea pig is greater than pressure of the endolymph. The heat regulating factor of the arteriovenous arcade of the spiral ligament may play a role in this difference of pressures.

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XLII

EXPERIMENTAL INNER EAR PRESSURE CHANGES

FUNCTIONAL EFFECTS

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The most widely accepted theory for the explanation of the auditory effects of Ménière's disease, namely, that the loss of hearing is due to an endolymphatic cochlear hypertension, is a plausible one, but experimental evidence that an increase in pressure in the inner ear can cause a hearing loss has been lacking.

Indeed, experiments to date have pointed in the opposite direction, but a careful examination of these experimental efforts reveals that they may not have eliminated the possibility of endolymphatic hypertension producing a deafness.

To Williams,¹ Békésy's² experiments cast doubt on the theory that increased pressure of perilymph and endolymph could produce loss of hearing. Békésy, however, in the experiment cited, demonstrated only that by increasing intracochlear pressure, neither the stapedial footplate nor the round window membrane was fixed from within and that hearing loss could not accrue from this. Békésy did not rule out the possibility of hearing loss by interference with or inefficiency of basilar membrane vibration, or of compression of the organ of Corti which might interfere with torsion or bending of the hair cells. Lempert and his co-workers³ raised the pressure of perilymph in the lateral semicircular canal and found no decrease in

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the cochlear microphonic response of the monkey. To assume from this that increased inner ear pressures cannot cause deafness requires the assumption that pressure at the anterior end of the labyrinth where the microphonics were produced, was the same as that far posteriorly, where the pressure was applied, and that there is no perilymph relief point in the monkey, so that endolymphatic pressure may be always considered equal to perilymphatic pressure. The experiment in this regard would be more compelling if the pressure were applied anteriorly in the labyrinth, and more than one animal were tested. Tasaki and his co-workers⁴ injected 0.015 mm^3 into the scala media of the guinea pig and found a rise of 5 microvolts in the DC potential upon injection, and a drop in potential upon aspiration. What effect this had upon hearing could not be adduced, because action potentials were not recorded. Even assuming a perfect seal by tissue tension of the stria vascularis around the pipet, injection of this amount of fluid would produce a negligible pressure rise if any in the scala media. Fernandez⁵ has estimated the volume of the guinea pigs scala media at roughly 2 mm^3 ; by these figures injection of 0.015 mm^3 would increase the volume of that compartment by less than 1%. It is not reasonable to assume that any pressure effect on the organ of Corti or downward displacement of the basilar membrane would occur in the guinea pig before a completely relieving upward displacement of the thin, highly flexible Reissner's membrane would occur, when dealing with volume displacements of small magnitude. Indeed, the temporal bone sections of patients with Ménière's disease commonly demonstrate a Reissner's membrane filling the scala vestibuli without any downward bowing of the basilar membrane. Misrahy and his co-workers,⁶ using a similar technique, found that amounts of fluid ranging from 0.0004 to 0.0015 mm^3 can be injected into the scala media "with impunity." It seems evident that small pressure changes in the cochlea could not be expected to produce changes in hearing since Reissner's membrane and the perilymphatic aqueduct are relief points, and if changes can occur due to pressure, this pressure must be of a relatively high order.

Because of a seemingly basic disagreement between what has been found experimentally and what appears anatomically to be the cause of deafness in Ménière's disease, an animal experiment was designed to approximate in an acute manner what has been described in Ménière's disease in an attempt to shed further light on the question. The experimental effort was directed towards producing a graded increase

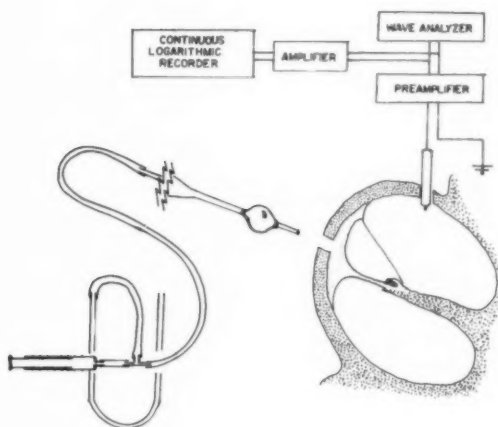


Fig. 1.—Experimental method. The micropipet, at center of figure, is represented only in its lower portion. A rounded flange fashioned from epoxy glue was allowed to harden and served to prevent major back-flow of fluid from the inner ear. Air pressure was applied to fluid in the pipet from a syringe, and monitored by a simple water manometer system. The apparatus recording responses was arranged as pictured. The arrangement for applying sound pressure to the tympanic membrane is described in the text.

in pressure inside the cochlea, while continuously recording the cochlear AC potentials.

PROCEDURE

Micro-pipets were mechanically drawn from glass tubing heated regionally by a nichrome wire coil through which a DC current was passed. The pipet diameter and rapidity of the taper were found to be a function of the volume of glass heated and speed of the pull. Pipets used ranged from 40 to 90 micra at the tip, with a fairly rapid taper in order to apply firm pressure between an epoxy bead flange (Fig. 1) and the margins of the hole in the otic capsule. A hole was drilled over the stria vascularis of the second turn or third turn for the insertion of the micropipet. The micropipet tip was driven with a micromanipulator slowly through the stria vascularis, while con-

tinuously recording the cochlear microphonic, until the tapered shoulders of the epoxy flange abutted firmly the margins of the hole. The design was to flange the pipet so as to allow the pipet mouth to rest nearly in the center of the scala media. The pipet was filled with a high-potassium low-sodium isotonic solution with a pH of 7.35. Electrolytes were in a concentration as close as possible to that determined by Smith⁷ for guinea pig endolymph.

Graduated pressure was applied to the contents of the pipet by a syringe through tigon tubing. The pressure was monitored through a side-arm connected to a water manometer (Fig. 1), so that increments of pressure from 5 cm to 50 cm of water could be applied. A pipet of each size used was calibrated for determination of the amount of water pressure at the pipet mouth at different manometer pressures, because the high degree of surface tension in tubes of such small caliber obviously does not permit the pressure applied to be equal to the pressure delivered. A minimum of 10 cm of water pressure was necessary to obtain any flow at all, and after this, the pressure at the small end was roughly two-thirds the pressure at the large end. Pressures were calibrated against a second water column. Bits of debris at times clogging the narrow ends of pipets posed a problem not entirely solved even by ultrafiltration of the injected fluid. Leakage of some fluid around the epoxy flange at high pressures was present in six of the seven animals usable for data collection. Without the epoxy flange, escape of fluid around the pipet occurred so freely that it was doubtful that any rise in pressure was imparted to the inner ear fluids. Because of some leakage even with the flanged pipet, pressures inside the inner ear could not be read directly from the corrected manometer, but were perhaps 10% to 20% less depending upon the degree of leakage. Where an elliptical or irregular hole allowed major escape of fluid thus precluding any pressure increase, the animal was discarded.

A loud speaker unit mounted outside a shielded, soundproofed room was driven in the usual way by an oscillator-attenuator-power amplifier system. A hard rubber tube conducted the sound from the speaker unit through the shield and walls of the room to the animal operating area. This tube was terminated by a small hard-rubber cannula which contained concentrically the probe tube of a calibrated WE640AA condenser-microphone-probe-tube system which furnished the data for determining sound pressures. The cannula and its con-

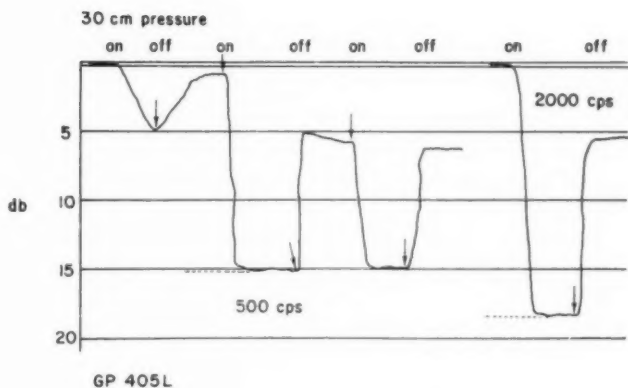


Fig. 2.—The continuous recording (schematic) of GP 405L. Time on abscissa and response in decibels on ordinate. Pressure was held on for 10 to 20 seconds each time. Failure of responses to return to the reference level (0 db) was usually due to shorting of electrodes by fluid accumulation in the bulla. The dotted lines represent the noise level in each case.

centric probe tube were small enough to be tied into the external canal of the animal so as to form a completely closed system with the speaker unit at the other end.

The cochlear microphonic responses of the animal were picked up by a stainless steel electrode insulated in all but the tip portion which was inserted through a drill hole into the scala vestibuli of the first turn. The indifferent electrode was placed in the neck musculature. These potentials were amplified exactly 1000 times by a battery-powered amplifier and then conducted to a GR 736 A waver analyzer outside the room. Potentials were also monitored continuously on a logarithmic recorder so that the responses could be read directly in decibels.

Healthy, normal guinea pigs were used for these experiments. They were deeply anesthetized with a solution of diallyl barbituric acid with urthane administered intraperitoneally. The bulla was exposed and entered through a ventral approach. The recording elec-

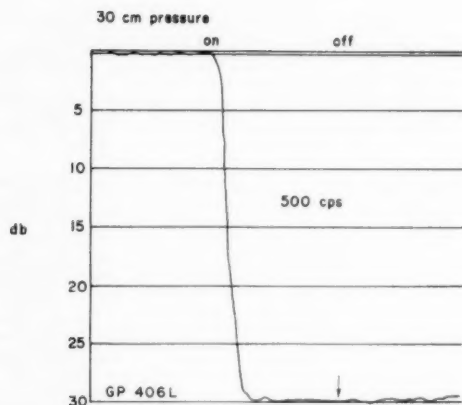


Fig. 3.—Continuous recording (schematic) of GP 406L. Time on abscissa, response in decibels on ordinate. Duration of recording above represented is about 30 seconds. Upon failure of return of response when pressure was released, the sound pressure at the tympanic membrane was repeatedly increased but no response could be elicited. The animal's ear had been killed.

trode was inserted and an intensity function obtained at the frequencies to be used for that experiment. The sound level was then set to give a certain level of response, usually about 100 microvolts, and the continuous recorder started. The recording then monitored the drilling of the pipet hole, insertion of the pipet, and induced pressure changes. At the termination of the pressure change a second intensity function was obtained.

RESULTS

Eleven guinea pigs were used in the experiment, and of these, seven could be used for data collection. In the remainder, technical difficulties supervened to the degree that data were unreliable or uncollectible.

In the first animal (GP 405L), recording at 500 cps, the first application of 30 cm of pressure produced a slow drop of 5 db below

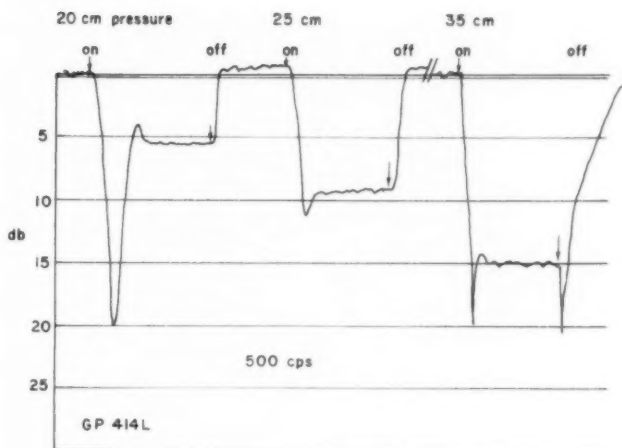


Fig. 4.—Continuous recording (schematic) of GP 414L. Time on abscissa, response in decibels on ordinate. Pressure increments are shown to produce an incremental decrease in response. Figure 5 shows position of the pipet tip in this animal.

the reference level with recovery to 2 db below this after release (Fig. 2). After adjusting the pipet fit, 30 cm was again applied and cochlear potentials dropped immediately to noise level, 15 db down. Release of pressure immediately resulted in a rise to 5 db down. Thirty cm was again applied after the potentials stabilized, and the response again dropped to noise level. Release of pressure brought the response back to 7 db down. Pressure of 30 cm was again applied while recording at 2000 cps, and responses immediately dropped to noise level at 18 db down. Release of pressure brought the response back to 6 db down. It is important to note that each pressure application (save the first) was accompanied by a loss of all recordable microphonic activity. This animal was not saved for histological examination.

The second animal (GP 406L) was a middle-aged (674Gm) guinea pig but we were unprepared for the result. Insertion of the pipet resulted in an unusual, perfect fit with no leakage. While



Fig. 5.—The second turn of the cochlea of GP 414L. The tract of the pipet can be seen. The stria vascularis has not been penetrated, and the spiral ligament has been pushed toward the modiolus by the pressure increase.

recording at 500 cps, 30 cm of pressure was applied and potentials immediately dropped to noise level (Fig. 3). Release of the pressure resulted in no gain in hearing. Steadily increasing the sound pressure at the tympanic membrane failed to elicit any response from the ear. The animal's ear had been killed. Unfortunately we do not know what killed it because the animal's ear was not saved for histological examination.

In GP 414, pressure increments were applied and this resulted in an incremental decrease in response (Fig. 4). It stabilized at a 6 db loss no 20 cm of pressure after a sudden brief dip to 20 db down, and rose above the reference level quickly upon pressure release. With 25 cm pressure, the response rapidly stabilized at 10 db down and returned to the new reference level at once after release of pressure. The application of 35 cm of pressure produced a 15 db drop,



Fig. 6.—Histological section indicates the entry of the pipet into the scala vestibuli of the second turn in GP 419L.

with a rather slow return to the reference level after release of pressure. At this point, it was found that the animal's ear was overloading early, indicating some degree of inner ear damage. The temporal bones of this and the following animals were saved for histological examination. The temporal bones were fixed, decalcified, imbedded and sectioned, then mounted in serial fashion and stained in the usual manner. The histological findings in this animal, GP 414L, were most amazing and dramatically demonstrate the absolute necessity of checking histologically for the anatomic effects and location of the lesion created whenever cannulation of the cochlear compartments is carried out. This temporal bone showed the spiral ligament pushed away from the bony wall of the cochlea compressing the cochlear duct against the modiolus (Fig. 5). My intent had been to cannulate the scala media but the stria vascularis had not been penetrated. In this animal, then, although the scala media pressure



Fig. 7.—Histological section indicates the entry of the pipet into the scala tympani of the second turn in GP 422L.

was probably raised by this compressive action, the consequent interference with basilar membrane vibration would seem to be the major cause of the reversible loss of response.

The response of GP 419L was similar to the animal above, 20 cm of pressure producing a 5 to 8 db loss, and 40 cm producing a 10 db to 15 db loss, with each decrement of response reversible. The tip of the pipet in this case was found to have come to rest in the scala vestibuli (Fig. 6).

The slow response and incomplete recovery of GP 422L to 20 cm pressure (18 decrement with an 8 db recovery) was thought to be due to a partially obstructed pipet permitting only a slow flow rate through it, and a relative hypoxia altering the response of the inner ear. The condition of the animal at the time of pressure application



Fig. 8.—Histological section indicates the entry of the pipet into the scala vestibuli of the second turn in GP 417L.

was poor. The pipet in this animal was found to have come to rest in the scala tympani, after piercing the basilar membrane (Fig. 7).

In GP 417L the pipet was introduced into the scala vestibuli of the second turn and proven by examination of the sections (Fig. 8). The responses in this animal varied according to the pressure applied as in the other animals.

The remaining last animal in the series showed a response similar to those above.

COMMENT

A number of possibilities to explain the change in the electrical activity of the inner ear under the conditions of the experiment

require consideration. Many other factors besides pressure changes within the cochlea may have been operative, any one of which could have caused or contributed to the decrease in cochlear potentials reported. Each of them require careful examination.

1. *A Short-Circuiting of Electrodes.* The active electrode may produce a short-circuit by coming into contact with the wall of the bulla and is prevented by thorough insulation of the shaft all the way to the tip of the electrode, which rests entirely within the scala vestibuli. Shorting of the side of the tip against the margin of the hole in the otic capsule would also add a parallel resistance to the system and a consequent voltage drop. This was a hazard occasioned by slight movement of the animal's head when micromanipulator pressure was applied to the pipet, and was constantly guarded against. If leakage of perilymph and loss of injected fluid was allowed to accumulate in the bulla to the level of the scala vestibuli hole, this would ground the active electrode out. Constant attention was necessary to maintain a dry field.

2. *Elicitation of Intratympanic Muscle Reflex.* The immediate loss of response was held as long as pressure was held, and showed no tendency to decay. When pressure was released, the response usually came up immediately. Neither of these are characteristic of muscle reflexes.

3. *Introduction of a Temperature Change in the Inner Ear Fluids.* The fluid injected into the scala media was at room temperature, but since the bulla was open to room air circulation for at least an hour before injections were commenced, the differential was probably less than 20° F. The total volume injected as compared to the mass of the cochlea, although not measured, was undoubtedly quite small. Further, the rapidity of recovery upon release of pressure militates against this as a factor.

4. *Alteration of the Conductivity of Inner Ear Fluids* by alteration of electrolyte concentration. The reversibility of the loss of response makes this an unlikely explanation. The electrolytes injected would undergo rapid diffusion and thus become non-recoverable.

5. *Toxic Effect of Injected Fluid upon the Hair Cells.* It was thought the best guard against this was the careful preparation of

the injected fluid. If toxicity nonetheless were a factor, it could not have been major because the rate of recovery from cellular poisoning is a gradual process.

6. *Change in the DC Potential* between perilymph and endolymph, or endolymph and stria vascularis. Little is known that is certain about the interrelationship of the DC and AC cochlear potentials. Although changes in the DC potentials may have been a factor here, these were not measured because it would have required more holes in the cochlea, thus adding further variables. Our interest lay primarily in any change engendered in action potentials.

7. *Pressure Change Inside the Cochlea.* There are a number of ways in which pressure could have produced a change in action potentials.

a. Mechanical effect on the basilar membrane. Bekesy's experiments suggest that this is unlikely. With even intense pressure applied to the perilymphatic system, he found that the round window membrane vibrated normally in response to ossicular vibration, presumably also vibrating the basilar membrane. A change in normal pattern or damping of basilar membrane vibration, however, is not ruled out by this, and remains a possibility here.

b. Rupture of Reissner's membrane with a mixture of perilymph and endolymph. This occurrence is made unlikely by the facility and degree of recovery upon pressure release. If humoral mixture had dropped the response, there would be nothing to separate the humors again until the tear repaired itself. This may have occurred to GP 406L in which the response did not recover.

c. Compression of blood vessels of the stria vascularis producing hypoxia. This is unlikely because both the loss of response and recovery are gradual when due to hypoxia.

d. Compression of hair cells so that they cannot distort normally. Compression of the organ of Corti down upon the basilar membrane is the picture seen in many of the histologically sectioned temporal bones⁹ from patients who suffered from Ménière's disease, and would appear to be the most reasonable explanation for the reversible loss of response seen in these experimental animals. The *modus operandi*

is probably the limitation of the distorting effect the vibrating basilar membrane has upon the hair cells, by virtue of the increased endolymphatic pressure, imparted by increased perilymphatic pressure. If perilymphatic pressure is increased, endolymphatic pressure must also be increased, because it is obvious that Reissner's membrane is incapable of resisting hydrostatic pressures of any magnitude. This could effectively limit action potentials temporarily, while physical compression was present, without necessarily injuring the cell so that it could not immediately respond once the compression was released.

The difference in experimental results between what was found here and what other investigators have found would seem to be best explained on the basis of the difference in location of pressure application or degree of pressure applied. These results are compatible with current concepts of the pathophysiology of Ménière's disease.

SUMMARY

Because of the conflict between the generally accepted theory which holds that the loss of hearing in Ménière's disease is due to an overabundance of endolymph producing a hydrops, and experimental evidence which has failed to show a hearing loss due to increased intracochlear pressure, an experiment was designed in an attempt to resolve the conflict by approximating the conditions which seem to obtain according to the histopathologic picture of Ménière's disease. The cochleas of a number of guinea pigs were injected with a high-potassium low-sodium solution in such a manner as to produce a graded increase in intracochlear pressure. The cochlear AC potentials were simultaneously recorded. The responses were found to decrease according to the pressure applied, and return upon release of pressure. Various other explanations for the observed decrease in potentials in the experimental animals are discussed and shown to be unrelated.

OUT-PATIENT BLDG., ROOM C-6216

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XLIII

AGE, NOISE AND HEARING LOSS

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Impairment of hearing caused by exposure to noise, whether in industry, in military service, or in sport, is a problem of increasing importance in otology. Several rules have been elaborated for the calculation of the percentage of impairment of hearing from pure tone audiograms. In particular the principles developed by the Subcommittee on Noise of the Committee on Conservation of Hearing have gained rather wide acceptance.^{2,16} In those principles, however, one point was left incomplete. It was stated² that an allowance for presbycusis should be made, but, for lack of adequate information on the possible interaction of age and noise, no specific rule for making such an allowance was proposed.¹⁶

Since this manuscript was completed the work of Motta and Profazio¹³ has been brought to our attention. It is a pleasure to note the complete agreement in our observations and conclusions concerning 1) the independence of the effects of age and of noise exposure, 2) the time course of the development of noise-induced hearing loss, and 3) the presence of loudness recruitment with good discrimination for speech in noise-induced hearing loss.

In order to close this loophole and also to study the effect on hearing of exposure to different levels and spectra of noise the

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Reserach Center of the Subcommittee on Noise undertook several years ago a systematic study of the hearing of workers in certain industries where working conditions and techniques had been so stable that both the levels and the spectra of noises had been constant for many years, and where the turnover of personnel had been small. Analysis of the data collected on this project now gives us new insight into the development of hearing loss with prolonged habitual exposure to noise. It also shows that noise-induced hearing loss is independent of the changes in hearing associated with aging.

CHANGES IN HEARING LEVEL WITH AGE

Everyone grows older year by year but not everyone is exposed to noise that is sufficient to cause a permanent threshold shift. It is therefore easier to isolate first the effects of aging, by studying individuals who have had no significant noise exposure. Such a group of professional men was found in an organization in Los Angeles. The hearing thresholds for air conduction were obtained on over 95 per cent of this particular group, 1,300 in all. The inclusion of nearly all members of the group frees the sample from the bias of self-selection which has contaminated many other samples that have been used in the past for estimating the change of hearing level with age. From these 1,300 were selected 325 men who had had very little noise exposure.

The details of this study have been presented elsewhere.^{7,8} Figure 1 summarizes the final outcome, in the form of a series of smoothed curves that show the threshold shifts at 1, 2, 3, 4, and 6 kc. The shifts are measured from the mean hearing levels of the youngest group (18-20 years) as the reference levels. This use of a "biological baseline" eliminates the effect of many possible sources of error including the calibration of the audiometers, the methods of testing and the individuality of the technicians. The data reveal clearly the effect of aging from 20 to 70 years. The hearing levels rise more and more rapidly with age and also more rapidly the higher the frequency. The numerical values actually agree rather well with those obtained by Bunch 35 years ago.¹

TYPES OF PRESBYCUSIS

The poor hearing of elderly people is proverbial, and the term "presbycusis" was invented to describe this condition. The term

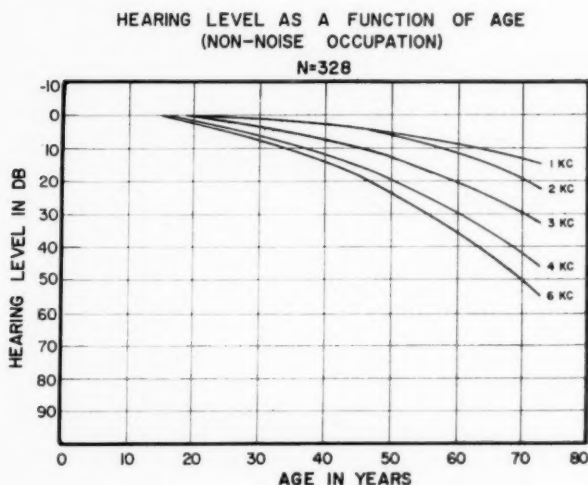


Figure 1

has gradually been extended to include all changes in hearing that are associated with the aging process. It appears useful now, however, to subdivide the concept according to the part of the auditory system which seems to be chiefly affected.

Much of the impairment of hearing in elderly people is quite clearly due to changes in the central nervous system, and it often seems to be associated with a dulling of other sensory faculties. A prominent symptom is poor understanding of speech. Another is shortening of the span of attention and another is a general slowing of the mental processes which contributes to the poor understanding. These changes are seldom significant before 75 years of age, and we shall dismiss them for the remainder of our discussion.

In the inner ear, a loss of fibers of the auditory nerve and also, perhaps as an independent condition, a loss of hair cells in the organ of Corti have both been associated with old age.^{3,15} These changes were seen more often in elderly individuals than in young people but not all the old people studied showed these anatomical changes by any

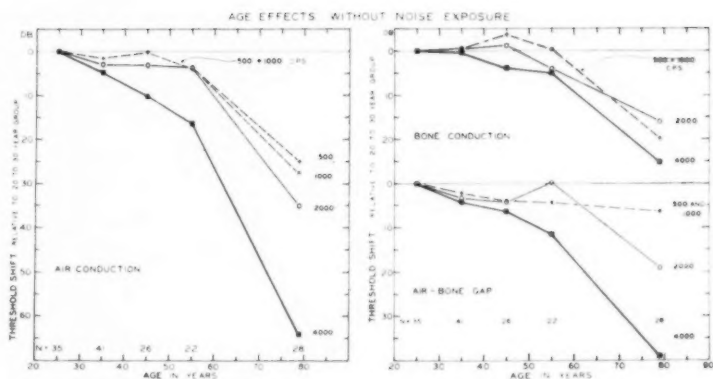


Fig. 2.—Comparison of air conduction and bone conduction thresholds in 164 men between twenty-five and eighty years of age, with history of no noise-exposure. Note the air-bone gap as a function of age and frequency.

means, even among those who showed the typical high-tone hearing loss. Crowe, Guild and Polvogt, in their classical paper,³ stated clearly that their correlation of visible pathology with gradual high-tone hearing loss was far from perfect. Nevertheless it was probably their finding that degenerative changes may be present in old age that has led to the general impression, reflected by one of us in a recent textbook⁴ and by Pestalozza and Shore,¹⁴ that presbycusis is a progressive sensory-neural hearing loss that develops first and most severely for the high frequencies. If this interpretation were correct presbycusis would closely resemble noise-induced hearing loss. Actually, on this basis, it has been stated specifically by experts that it is impossible to separate these two conditions by any known audiometric tests.

Another theory of the effect of aging (presbycusis), clearly stated by Mayer,¹² attributes the threshold shift to a physical change in the inner ear, presumably a stiffening of the cochlear partition.^{6,10} It is true that Crowe, Guild and Polvogt³ reported some calcification and hyalinization at the extreme basal end of the basilar membrane in a few of their specimens from elderly patients, but not enough to account for the hearing losses measured before death. If this

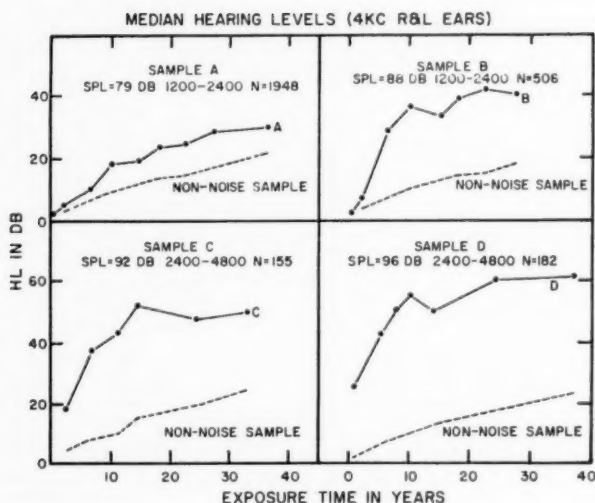


Figure 3

theory invokes changes in the stiffness of the basilar membrane, it encounters some difficulty in regard to the action of the cochlear partition as an acoustic analyzer, the sense of absolute pitch, and the greater loss for high-tones in presbycusis; but the theory has not been developed in detail.

The possibility that physical changes with age might occur in the middle ear has scarcely been considered. Pestalozza and Shore implicitly rejected this possibility when they excluded from their study of presbycusis,¹⁴ all cases in which hearing levels were higher by air than by bone conduction.

CONDUCTIVE PRESBYCUSIS

To test the hypothesis that the effect of aging is a purely sensory neural loss, the Research Center re-tested 124 of its group of professional men. This time all subjects who had had any military service whatever were excluded. Threshold levels were measured for bone

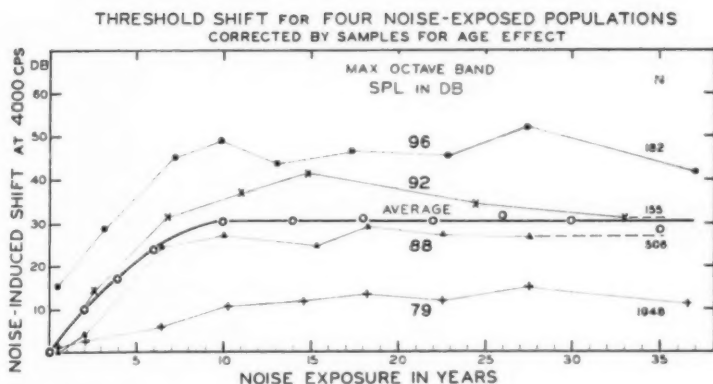


Figure 4

conduction, as well as for air conduction, at the frequencies 500, 1000, 2000 and 4000 cps. The results are summarized in Figure 2, using the mean thresholds of the 20 to 30 year old group as the reference levels. Few of these subjects were over 60 years old; however, to extend the range of old age a group of inmates at a home for old soldiers was similarly studied. Most of these men had served in the armed forces before World War I but it was ascertained that few of them had engaged in actual combat or had suffered noise exposure that was severe by modern standards.

In this carefully screened sub-group without noise exposure the high-tone threshold shift with age is rather less, by air conduction, than it was for the larger group, but the shift is nevertheless very definite at 4000 cps at 55 years. The 79 year group shows much greater shifts at all frequencies.

The unexpected results are a relatively small shift at 4000 cps by bone conduction and the presence of a very significant air-bone gap. Evidently the high-tone threshold shift that occurs with age is not primarily sensory-neural but is largely a conductive loss in the middle ear. We make this general statement without speculating as

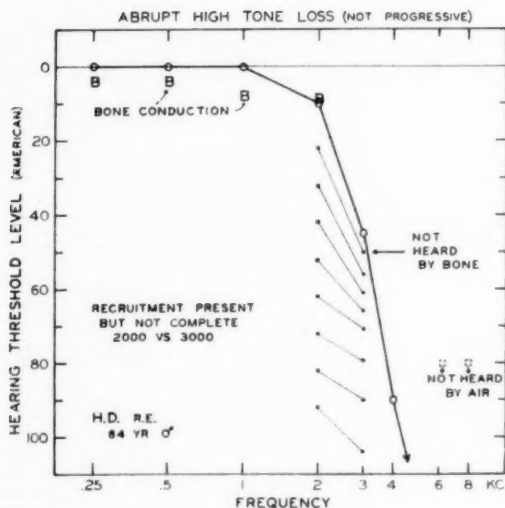


Figure 5

to the exact mechanism of a conductive loss that is greater the higher the frequency. Such a relation is perfectly possible, however, and the conductive presbycusis that is revealed by the air-bone gap in Figure 2 must be attributed to the middle ear.

Mayer's hypothesis¹² involved a conductive impairment of the inner ear. The idea of conductive impairment in the inner ear is unfamiliar but it is perfectly logical. Any physical change in the tissues that attenuates the acoustic energy anywhere along its pathway before it reaches the hair cells will produce a conductive hearing loss. Even a loss of efficiency in the final step of bending the hairs and thereby releasing the electrical energy of the cochlear microphonic will amount to the same thing. The sensory cells are finally activated normally but more initial acoustic energy is needed to do the job. (We cannot identify a hearing loss as sensory-neural until we can demonstrate either loudness recruitment, a discrimination loss, or total loss of hearing for very intense sound.)

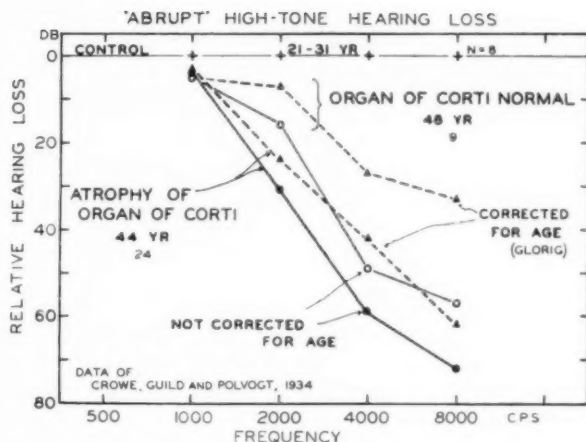


Fig. 6.—Comparison of "abrupt" high tone hearing losses with, and without hearing losses with, and without demonstrable microscopic changes in the organ of Corti.

NOISE-INDUCED HEARING LOSS

Noise-induced hearing loss, on the other hand, is sensory-neural. It does show loudness recruitment by the monaural two-frequency balance test. In a very recent study at the Research Center, recruitment was usually complete or very nearly so both in industrial workers with many years of habitual noise exposure and in policemen who had incurred hearing losses from shooting pistols in target practice. (The details of this study will be published elsewhere.) All of these subjects, incidentally, had very good discrimination for speech in spite of rather extensive high-tone hearing losses. (This type of simple loudness recruitment must be carefully distinguished from Ménière's syndrome, in which loudness recruitment is associated with poor discrimination for speech, tinnitus, loss of tone quality, etc.)

Thus noise-induced hearing loss is fundamentally different from most of the threshold shift associated with age. The two conditions arise in different parts of the auditory mechanism. One is sensory-neural, the other is conductive.

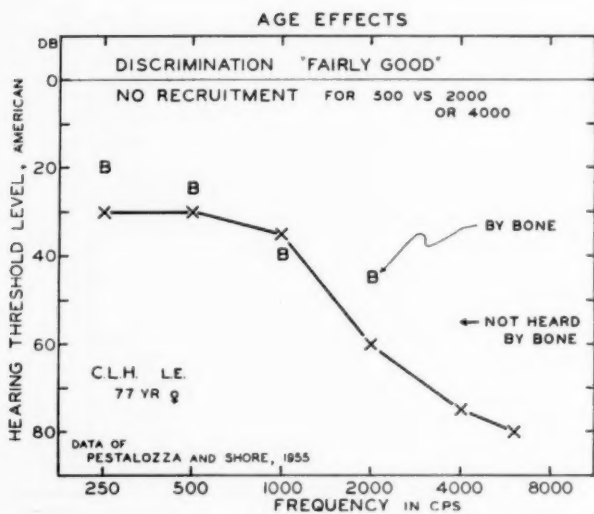


Figure 7

We can now correct for the age effect and see in pure form the effects of noise exposure on the hearing of men who have worked for many years in particular industrial noises. Four samples of such workers were available. They had worked in noises with sound pressure levels (in the most significant octave band) of 79 db, 88 db, 92 db and 96 db respectively, some of them for as long as 40 years. The air-conduction thresholds of these workers were measured by technicians who were closely supervised by the Research Center (Fig. 3). The data from each sample were grouped according to the years of exposure of the subjects. For each five or ten year group in each sample the mean age was calculated.

In this figure, and in the following discussion we pay attention only to the hearing levels at 4000 cps, where the permanent threshold shift induced by most industrial noises is greatest.

The corrections for age for each group, derived from the curve shown in Figure 1 and indicated by the dashed lines in Figure 3, were

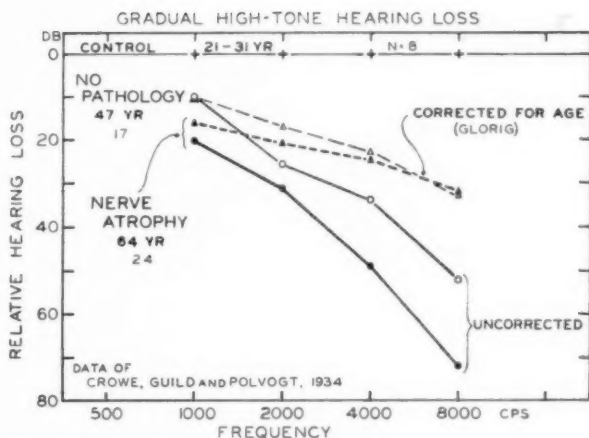


Fig. 8.—Gradual high tone hearing loss (cf. Fig. 6). 1) The median age of the group with normal auditory nerves is about the same as for the abrupt type of normal organ of Corti. 2) The median relative hearing loss of this subgroup when corrected for age are not very abnormal and are much like those of the corresponding "abrupt" subgroup. 3) The median age of the group with nerve atrophy is sixty-four years: twenty years older than the corresponding "abrupt" group. 4) When corrected for age the median relative hearing losses are nearly identical with those of the subgroup with no pathology, and not very abnormal.

subtracted from the permanent threshold shift of each subgroup, thus, statistically at least, the effects of aging were eliminated. Figure 4 shows the progressive shift of median hearing level for each of the four samples, corrected in this way for age. As before, the reference level is the hearing level of non-noise exposed young men, measured under the same conditions and by the same technicians. The central heavy curve represents the average threshold shift of all four groups, based on the ordinate values of the other curves at the two or four year intervals indicated by the circles.

It is perfectly obvious, particularly from the average curve, that the noise-induced component of the hearing loss reaches its maximum in about ten years of exposure time and remains constant thereafter for exposure times up to 40 years. The curves for the separate sam-

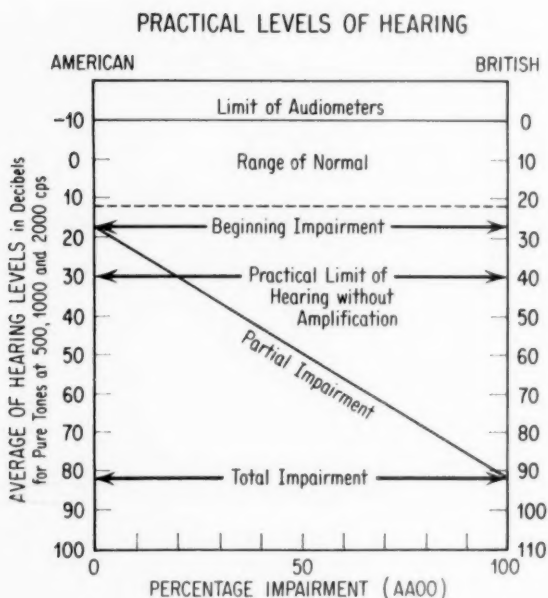


Fig. 9.—Practical levels of hearing for everyday speech relative to American and British audiometric zero reference level. (Taken from *Hearing and Deafness*, by H. Davis and S. R. Silverman, Revised Edition, New York: Holt, Rinehart & Winston, Inc., 1960.)

ples show how the level at which the noise-induced component of the hearing loss stabilizes is a function of the sound level of the noise. Of course the actual measured hearing levels of these men continue to rise slowly during their later years of exposure but that increase is simply the effect of age which is superimposed on the noise-induced shift (Fig. 3).

COMMENT

We will point out a few of the implications of these various observations. First of all, the aging process is independent of injury by noise. The age effect continues during the development of the

noise effect and after the noise effect is complete. Furthermore, aging does not sensitize the ear to injury by noise as some have feared.¹¹ Also, once a worker has completed his permanent threshold shift, in about ten years, he may just as well continue to work indefinitely in that or any lesser noise; but if he moves into a more intense noise he should expect a further increase in his permanent threshold shift.

Let us return to the question of the nature of the effects of age on the ear. It is clear that there is not just a single effect but several; which, indeed, should not surprise us. We have identified one that has apparently been overlooked, in the middle ear. Its presence is proved by, and its effects on hearing is measured by, the air-bone gap. It is a progressive high-tone conductive hearing loss that begins to develop in middle life.

However, not all individuals suffer from much conductive age effect. Pestalozza and Shore¹³ found 24 elderly individuals with high-tone hearing loss (presbycusis) among the clientele of Central Institute for the Deaf whose hearing levels by air and by bone conduction were equal, at least up to 1000 cps. Some had an air-bone gap at 4000 cps, but in many cases the high-tone losses must be attributed to their inner ears, their auditory nerves or their central nervous systems. These 24 subjects returned for more extensive hearing tests, including monaural loudness balance tests for loudness recruitment. Five showed partial recruitment, but 10 members of the group showed no recruitment of more than 5 db. Five were unable to make consistent loudness balances. Four, but only four, ears showed complete recruitment.

We discount the four cases with complete recruitment because their audiograms show steep abrupt dips and not the gradual slope that is most characteristic of advancing age. Instead they had deep, rather abrupt 4000 cps dips. We point out that the 4000 cps dip is the most characteristic pattern of noise-induced hearing loss, and it is also closely related to the "abrupt" type of audiogram identified by Crowe, Guild and Polvogt.³ Let us consider this abrupt type of audiogram for a moment. It is illustrated in Figure 5. Crowe, Guild and Polvogt showed that the abrupt type of audiogram, particularly if 8000 cps is not heard, is associated with partial or complete loss of sensory cells from the basal end of the organ of Corti. Typically the neurons and the supporting cells also are absent where

the lesion is severe. However, this audiogram and this type of pathology in the inner ear appear in youth and middle age also and are not closely associated with age as such.

One of us (H.D.) is gathering further information on abrupt high-tone hearing loss. There are some indications that a hereditary factor is involved.

Let us return to the ten ears with no recruitment in the elderly group studied at Central Institute for the Deaf. These ears must have had inner conductive impairment, or else a systematic elevation of thresholds of all of the sensory units in the high-tone region that was tested for loudness recruitment, or else equal recruitment at the two frequencies that were compared, or quite possibly some variation of these changes. We believe that the most plausible interpretation is a physical change in certain tissues of the cochlear partition.¹⁰ The data from one of these cases are shown in Figure 7. It, like all the others, shows a "gradual" high tone hearing loss. This type of audiogram is the one which, in the Crowe, Guild and Polvogt series, was the type most clearly associated with age. But in that series only about half of the cases showed any significant visible cochlear pathology (Fig. 8). The loss of some nerve fibers may have contributed to the hearing impairment in some cases, but there is no good reason to suppose, as some have done,⁹ that there is any direct relation between auditory threshold and density of innervation of the organ of Corti. (A more complete discussion of the data of Crowe, Guild and Polvogt, and of a possible sex-linked genetic factor involved in abrupt high-tone hearing loss is in preparation by one of us [H.D.] .)

In summary concerning presbycusis, we identify four major age effects. One is central presbycusis. Another is the classical sensory-neural presbycusis which we believe has generally been overemphasized. A third is middle ear conductive presbycusis, and the fourth is inner ear presbycusis, which show considerable high-tone hearing loss by bone conduction. These age effects may occur in any combination. Strong supporting arguments for the existence of inner ear conductive presbycusis are 1) the complete independence of age effects from noise-induced sensory-neural hearing loss, and 2) the absence of loudness recruitment in many cases of carefully selected inner ear presbycusis.

RELATION OF AGE TO HEARING IMPAIRMENT AND TO WORKMEN'S
COMPENSATION FOR NOISE-INDUCED HEARING LOSS

The amount of threshold shift with age up to the age of 70 years that was summarized in Figure 1 and the excellent speech discrimination of workers with noise-induced hearing loss⁵ allows us to assess the importance of the age effect in relation to compensation for industrial hearing loss. Here it is necessary to make the primary assumption that compensation for impairment of hearing need not be paid simply because there is a measurable shift in the sensitivity of hearing but only when there is a significant handicap in the hearing for everyday speech.^{2,16} Otherwise said, compensation should be paid for practical impairment of hearing, but impairment does not begin at the zero of the audiometer scale.

In the United States there is increasing agreement that hearing impairment for purposes of workmen's compensation should be based upon the hearing threshold levels for the frequencies 500, 1000 and 2000 cps.¹⁶ These frequencies represent the bands most important for the understanding of speech. The recent speech tests on workers with high-tone hearing loss⁵ are a direct experimental confirmation of this principle. In spite of many severe 4000 cycle dips and many significant threshold shifts at 3000 cycles, the workers who were tested all, and we emphasize all, had very good scores on word discrimination tests that were even more difficult than the usual PB word lists.

The rule recommended by the Committee on Conservation of Hearing¹⁶ is that hearing impairment should be considered to begin only when the average hearing level for the three frequencies 500, 1000 and 2000 cps exceeds 15 db. Percentage impairment is considered to increase at the rate of one and one-half per cent per decibel, as shown in Figure 9, and impairment becomes total at an average hearing level of 82 db on the American scale.

The average age effect of itself does not produce hearing impairment in this sense by the age of 70 years. The average threshold shift for speech should be only 10 db. It is our personal opinion that no substantial injustice is done if no correction or allowance is made for the age effect when judging the percentage impairment for which compensation should be paid. The omission of such a correction or allowance may, it is true, represent a small bias in favor of the worker.

On the other hand, it may equally well be claimed that there is a small bias in the opposite direction that arises from neglecting threshold shifts above 2000 cps.

The question of how a correction for presbycusis should be applied if it is desired to do so may be an academic question, but it is of interest because the same question appears in all cases of mixed conductive and sensory-neural loss and in cases of "second injury." We have shown that the age effect is chiefly conductive and that noise-induced hearing loss is sensory-neural. The bone-conduction threshold levels may be taken as a reasonable index of the threshold shift that is sensory-neural. Monaural loudness balances are theoretically even better if it is practical to carry them out. But then the question arises of how to apply the correction. Should the number of decibels that is attributed to the conductive loss, which was obviously not caused by the noise exposure be subtracted first and then the hearing impairment calculated? A moment's reflection will show that such a rule might lead to considerable injustice. The average hearing level might, for example, be 30 decibels, and 15 decibels of this might be attributed to noise exposure and 15 to age or to some other cause. If the decibels due to conductive loss are subtracted, the remaining 15 decibels, according to the rule stated above, would not constitute hearing impairment and there would be no compensation. This is manifestly unjust, because the noise exposure clearly caused one-half of a threshold shift which has led to a very significant over-all impairment.

A good rule in this situation is to first calculate the percentage hearing impairment that exists, regardless of the causes. Then make another calculation of the percentage of the total threshold shift from the American audiometric zero that should be attributed to the noise exposure. The worker is then paid a share of the compensation that was originally calculated on the basis of his over-all hearing impairment. His share corresponds to the percentage of the threshold shift that can be reasonably attributed to the noise exposure. In the above example, the percentage impairment corresponding to an average hearing level of 30 db is 22.5 per cent. Half of the threshold elevation (15 db) is attributed to the noise exposure. The worker should therefore receive half of the compensation that corresponds to 22.5 per cent impairment. This "principle of proportional liability" is applicable not only to the problem of age effects, which, as we have

seen, are only minor, but to all other cases of multiple causation of a hearing loss.

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XLIV

EFFECTS OF
INTENSE SOUND, HYPOXIA AND KANAMYCIN
ON THE
PERMEABILITY OF COCHLEAR PARTITIONS

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The hypothesis has been advanced that noxious stimuli may increase the permeability of cochlear partitions.^{1,2} This increased permeability may play a contributory role in depressing cochlear potentials by altering the ionic composition of extracellular fluids and allowing neurotoxic compounds to reach the hair cells and nerve endings or both. The technique of positive polarography was, therefore, adapted to measure the permeability of cochlear partitions.³ The method consists essentially of measuring the diffusion current produced by the oxidation of various compounds at the tip of an active platinum electrode with an impressed voltage of +0.9 volts. A change in current flow is interpreted as an indication of a change in the concentration of oxidizable compounds (NaI, vitamin C and Thorazine®) at the tip of an active electrode. Results obtained from experiments with the normal guinea pig cochlea were interpreted as an indication that two partitions, the basilar and Reissner's membranes, were impermeable to vitamin C, NaI, and Thorazine. The third partition, *stria vascularis* or the blood-cochlear barrier, was permeable to NaI and vitamin C, but impermeable to Thorazine.

The purpose of this investigation was to determine whether intense sound, hypoxia, and kanamycin, known to impair cochlear activity, might also alter the permeability of the cochlear partitions.

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Dr. Brooks is a postdoctoral research trainee, Grant No. 2B-5264 NINDB.

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METHOD

Guinea pigs were used for all these experiments. The animals were routinely anesthetized with Dial® with urethane (diallyl barbituric acid with ethyl carbamate), the bulla opened, and the cochlea exposed.⁴ All measurements were restricted to the first turn. The technique of positive polarography and the equipment for cochlear studies have been described in detail in a previous paper.³ In the following experiments, however, the Tektronix Type-D amplifier and the Dumont Model-33 oscilloscope were replaced by a Tektronix Model 502 oscilloscope that was modified to sweep at speeds as slow as 1 cm/50 sec. The oscilloscope was carefully balanced for zero grid current and zero drift. The changes in current flow were visualized on the oscilloscope and recorded with a Polaroid Land camera (Fig. 1).

Mechanical trauma to the cochlea was accomplished by exposing the animal to a pure tone of 2000 cps. The intensity was increased slowly until the desired effects on the microphonics and on the positive endocochlear DC potential were observed. The permeability of the cochlear partitions was then measured.

Hypoxia was produced by inhalation of nitrogen for 5 to 7 minutes, during which time the microphonics and endocochlear DC potential were observed.

Correct placement of the electrode in *scala media* was verified again at the end of each experiment by the presence of the post-mortem negative DC potential.*

Kantrex® (*kanamycin sulphate*) was administered intraperitoneally in daily doses of 260-400 mg/kg for a period of three weeks to deafen the animals. The effect of the injection was judged by the presence or absence of the *Preyer-pinna* reflex and the amplitude of the cochlear microphonics. The microphonics and the positive endocochlear DC potential were measured by standard methods.⁷ The negative DC potential of the basilar membrane was measured at the

* This postmortem negative DC potential is limited to *scala media*. With anoxia the positive endocochlear DC potential disappears, reverses its polarity, drops to a minimum value of approximately -90 mv, and then may persist for several hours.^{5,6}

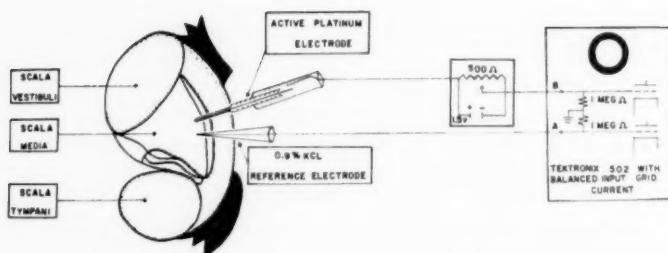


Fig. 1.—Schematic diagram of the positive polarographic technique to measure the passage of oxidizable compounds across the partitions in the guinea pig cochlea.

round window.⁵ The results were termed *questionable* when the observed increase in diffusion current following the administration of the compound showed an increase within the drift range of the amplifier and *negative* when no increase in diffusion current was observed (Fig. 2).

RESULTS

Hypoxia. Intravenous injections of NaI and vitamin C (*sodium ascorbate*) increased the diffusion current in both *scala media* and *scala tympani* in all of our experiments. Intravenous injections of Thorazine (chlorpromazine hydrochloride) definitely increased the current flow in only one of 33 experiments in *scala media* and 7 of 10 in *scala tympani*. In the remaining experiments results were questionable or negative. Injections of NaI directly into *scala tympani* increased current flow in *scala media* in 50 per cent of the experiments. No change in current flow was apparent in *scala media* following injections of vitamin C and Thorazine into *scala tympani*. Injections of NaI and vitamin C into *scala vestibuli* did not increase the current flow in *scala media*, in six of eight experiments with NaI and 10 of 12 with vitamin C. The other four experiments of the above series yielded only questionable results.

Intense Sound. Intravenous injections of either vitamin C or NaI increased the diffusion current in *scala media* and *scala tympani*. Thorazine, on the other hand, demonstrated no such effects in *scala*

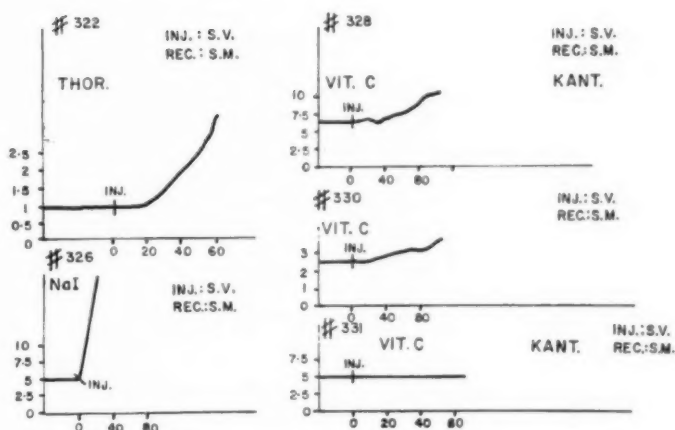


Fig. II.—Example of oscilloscopic traces following exposure to intense sound (Nos. 322 and 326), and injections of Kantrex (Nos. 328, 330, and 331). INJ = injection site; REC = recording site; Abscissa = time in seconds; Ordinate = current flow in 10^{-9} amps.

Numbers 322, 328 and 330 are examples of experiments showing a definite increase in current flow and are interpreted as the passage of compounds through Reissner's partition. Number 326 is an example of a false positive experiment. The instantaneous increase in current was probably due to sodium iodide leakage into *scala media* through a tear in the spiral ligament. Number 331 is an example of an absence of current increase due possibly in this case to a damaged electrode.

media and questionable, if any, in *scala tympani*, and then only after the most intense sound. Following the injections of any of the three compounds into *scala tympani*, the current flow in *scala media* was increased consistently if the sound was sufficiently intense to: a) reduce the amplitude of the microphonics by 75 per cent for NaI; b) reduce the positive endocochlear potential by 30 per cent for vitamin C; c) reduce the positive endocochlear potential by 90 per cent for Thorazine.

Similar results were obtained by injecting these compounds into *scala vestibuli*.

Kantrex.[®] Very few animals demonstrated overt or characteristic vestibular dysfunctions such as ataxia or loss of equilibrium. The microphonics were greatly reduced or nearly absent. The *Preyer-pinna* reflex was impossible to elicit in most animals. The positive endocochlear DC potential as measured in *scala media* was found to be greater than or equal to 70 mv. The negative DC potential of the basilar partition measured -50 to -90 mv. Intravenous injections of either NaI or vitamin C increased the diffusion current consistently in *scala media* and *scala tympani*. No such effects were observed with Thorazine. Vitamin C and NaI, but not Thorazine, increased current flow in *scala media* and when injected into either *scala vestibuli* or *scala tympani*.

COMMENT

Our results, interpreted schematically in Figure 3, show that the permeability of the cochlear partitions may increase following hypoxia, injections of Kantrex, and intense sound stimulation. In hypoxic animals the increase appeared greater at the vascular partition than at the basilar partition. No increase was observed at Reissner's partition. On the other hand, intense sound and Kantrex increased the permeability of the basilar and Reissner's partition but had little or no effect on the vascular partition. The effects of Kantrex differed from intense sound by an increase in permeability not associated with a decrease in the endocochlear positive DC potential. The presence of the positive DC potential and the diminished or absent microphonics in Kantrex-treated animals was similar to observations made by other investigators with the *mycin* family.⁸⁻¹⁰

The difficulty of detecting Thorazine in *scala media* in hypoxic guinea pigs may be explained in either of two ways. Either technical difficulties prevented the detection of small amounts of Thorazine in *scala media* as compared with *scala tympani*, or a functional difference may exist between *stria vascularis* and the blood-cochlear partition in *scala tympani*. The concept of a functional difference between the blood-cochlear barriers of *scala tympani* and *scala media* is consistent with the well-known biochemical and electrophysiological differences between these two *scalae*. The absence of increased permeability in Reissner's membrane in the hypoxic animal may be attributed to its probable low metabolic rate compared with the basilar membrane. A low metabolic rate would enable Reissner's partition to maintain

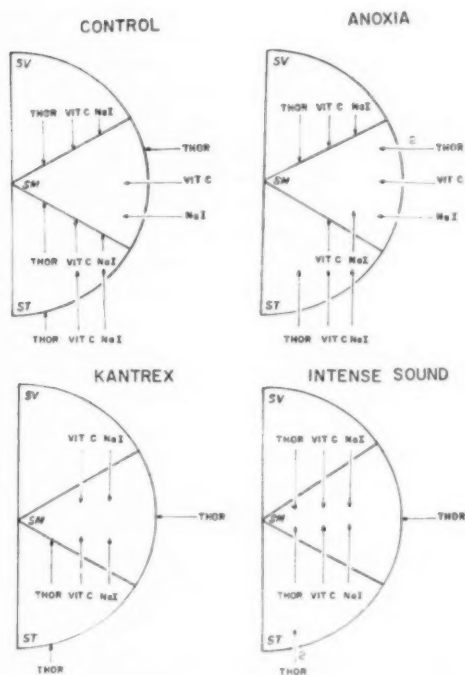


Fig. 3.—Schematic interpretation of permeability changes in the cochlear partitions induced by anoxia, Kantrex (kanamycin) and intense sound. The location of the compound on the schematic designates the injection site. Those located outside the three *scalae* indicate I.V. injections. ST = scala tympani; SV = scala vestibuli; SM = scala media.

Arrows start at the site of injection and point to the scala containing the electrodes. A broken line shows the partition permeable to the compound, a solid line = lack in permeability and ? = suggestive but not conclusive evidence.

normal intracellular oxygen tension in spite of the reduced oxygen supply, and thus the membrane would possess normal biophysical properties.¹¹

The changes in permeability of the basilar membrane under conditions of exposure to intense sound and hypoxia are consistent with the subtle differences of changes in electrical resistance described in an earlier paper.¹ The absence of an increase in permeability of the vascular partition under intense acoustic stimulation is consistent with the minimal changes in oxygen supply.¹² Finally, the over-all increase in permeability is consistent with the original hypothesis that increased permeability, with ensuing changes in chemical composition of extracellular fluids, plays a contributory role in the depression of cochlear potentials.

Such a hypothesis does not explain the high sensitivity of the hair cells to Kantrex in *scala media I*, with the lower sensitivity of the hair cells in the upper turns of the cochlea and in the vestibule.¹³ Possibly the hair cells in turn *I* are submitted to greater physical stresses and are consequently more susceptible to chemical injury. A more intriguing hypothesis may be based on the following findings:

1. The positive endocochlear potential was maximum in turn *I*, diminished in the upper turns and disappeared near the cochlear apex and in the vestibule.^{1,14,15}

2. The negative DC potential found in the basilar partition and the positive endocochlear DC potential were not affected by the action of Kantrex.*

3. Kantrex increased the permeability of the basilar partitions. This increase in permeability of the basilar partitions, unaccompanied

* A detailed description of the origin and function of the negative potential found in the basilar partition will appear in another paper.⁵ Briefly summarized, the experimental results pertinent to this discussion are: 1) the potential persists during anoxia and may even show an increase; 2) the potential can be affected by alterations in sodium and potassium concentrations of the endolymph and perilymph; 3) the potential plays an important role in the origin of the postmortem negative endocochlear potential found in *scala media* and possibly the aerobic and anaerobic microphonics; 4) a slight increase in the negative potential, often found in the early stages of hypoxia, coinciding with a diminution of the positive endocochlear potential, was interpreted as an indication of current flow across the basilar partition; 5) this potential is more resistant than microphonics to acoustic trauma.

by a change in the positive endocochlear DC potential or the negative DC potential of the basilar partition, may have induced a large current flow across the hair cells in turn *I*, with an *emf* of approximately 200 mv. In the upper turns and in the vestibule the *emf* and consequently the current flow diminished as the positive endocochlear DC potential decreased. It is conceivable that such a large current flow may have been injurious to hair cells. Maximum injury, therefore, has a tendency to occur in turn *I* where the current is maximum, minimum in the upper turns, and negligible toward the apex of the cochlea or in the vestibule.

This gradient in current flow when compounded with the direct cellular action of Kantrex may explain the difference in sensitivity of the hair cells to the ototoxic action of this antibiotic. A similar compounded effect of current flow with mechanical trauma may possibly help to explain the continuing cellular damage occurring days after exposure to intense sound.¹⁶

With hypoxia the danger of excessive current flow across the hair cells is less likely than with Kantrex, since the positive endocochlear DC potential disappears; consequently the damaging effect of hypoxia on the hair cells should be more uniformly distributed along the basilar membrane and vestibule.

An unexpected result was the lability of Reissner's membrane, hitherto considered generally as an inert partition. The increase in permeability with mechanical stress (exposure to intense sound) is of particular interest, since all mechanical receptors consist of bare nerve endings encapsulated with membranes of varying degrees of structural complexity.¹⁷ It follows that our results are in agreement with the concept that the origin of the generator potential at the peripheral end organ may be derived from chemical changes induced by a permeability change as a result of mechanical stress.¹⁸ This hypothesis agrees with the known high sensitivity of bare nerve endings to chemical changes and the susceptibility of nerve fibers to mechanical trauma.

SUMMARY

The technique of positive polarography was utilized to demonstrate changes in permeability of the cochlear partitions produced

by intense sound, hypoxia, and Kanamycin. Hypoxia primarily affected the permeability of the vascular partition. *Kanamycin* and intense sound primarily altered the permeability of Reissner's and the basilar partitions. Evidence is presented to support two working hypotheses:

1. The ototoxic effect of *kanamycin* and the traumatic effects of intense sound are potentiated by an increase in current flow across the basilar membrane.
2. The bare nerve endings found in mechanical receptors may be stimulated by a change in ionic composition secondary to a change in permeability produced by mechanical stress.

4570 SUNSET BLVD.

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XLV

THE EFFECT OF SENSORINEURAL LESIONS
ON PITCH DISCRIMINATION IN CATS

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In previous experiments on animals absolute intensity thresholds have been determined after creating sensory and neural lesions in the auditory system.⁶ The audiograms so obtained, when correlated with the histopathological data, extended our knowledge of the cochlea's excitation pattern and the extent to which neural elements may be missing before a loss becomes evident in the audiogram.

A logical extension of these studies is the determination of the extent to which such lesions affect auditory discrimination. While pure tone audiograms measure some characteristics of hearing, it is clear that they are incapable of reflecting the complete functional status of the auditory system. Certainly there is abundant clinical and experimental evidence that discrimination may be abnormal even though the pure tone audiogram is normal. It is now well established that pure tone audiometric thresholds of patients with tumors of the acoustic nerve may be normal or near normal and yet the speech discrimination very poor. On the other hand, in the case of auditory fatigue where the locus of temporary damage is the sensory cell, the audiogram may show large hearing losses, yet intensity discrimination may be improved.

Because the audiogram and discrimination tests may reflect changes in the auditory system differently, a specific study has been undertaken to determine whether damage to the neural elements or damage to the sensory cells will be differentially reflected by audiograms and tests of pitch discrimination.

From the Henry Ford Hospital Otological Research Laboratory. Supported by Grant No. B-1740 from the National Institutes of Health.

PROCEDURE

Two groups of cats were studied. In the first group partial cochlear nerve lesions were created, and in the second group sensory cell lesions were created. Prior to the creation of these lesions, one ear was rendered nonfunctioning by a surgical procedure and pure tone behavioral audiograms were obtained. These audiograms were determined with an avoidance conditioning procedure in which the animals were trained to move forward in a running cage whenever an audible tone was presented.

Lesions were created in four cats by partial section of the cochlear nerve in the internal auditory meatus. This was accomplished by an aseptic surgical procedure through the posterior cranial fossa in which the superior surface of the petrous pyramid was exposed and bone drilled away to uncover the neural complex deep in the internal auditory meatus. The facial nerve and the superior division of the vestibular nerve were retracted to expose the cochlear nerve at its exit from the modiolus. A small needle was used to cut predetermined amounts of the nerve, after which the surgical wound was closed and the animal given appropriate postoperative care.

In five cats, lesions of the sensory receptors were created by intense high frequency auditory stimulation. Several weeks prior to initiating auditory training, the auricle of the experimental ear was removed surgically and reconstruction performed so that the external auditory canal was easily accessible. This made it possible to connect a resonating tube and loud speaker system to the external auditory canal with a tapered, closely fitting, plastic tube about $1\frac{1}{2}$ cm in length. This closed system was capable of producing signal intensities above 150 db SPL (re .0002 dyne/cm²) at some of its resonant frequencies, as measured in the resonating tube at the point of exit of the plastic tube. The cats were anesthetized during exposure to the stimulation, and the tympanic membrane was examined before and after the exposure to make certain that it was not injured. Four of the cats were exposed to a 7,700 cps pure tone, and the fifth to several frequencies ranging from 7,700 to 25,600 cps.

Following creation of both types of lesions pure tone audiograms were taken periodically until the thresholds were stabilized (30 to 60 days), after which pitch discrimination thresholds were determined

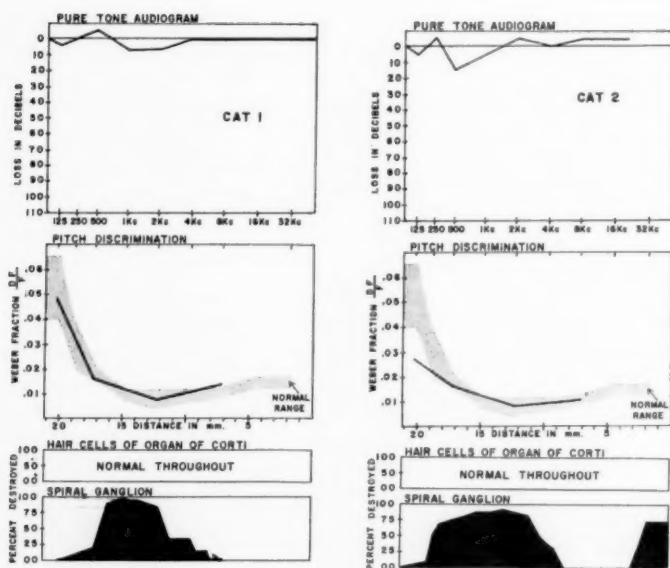


Fig. 1.—(A) Cat 1. The audiogram shows gain or loss in db from this animal's pre-operative thresholds. Pitch discrimination is plotted as the Weber fraction, with the stippled area indicating the normal range as determined on 8 normal animals. The frequencies in the two graphs are spaced in accordance with a previously determined anatomical frequency scale.⁷ The cochlear charts appear on parallel co-ordinates and show by black filling the severity and spatial distribution of the neural and sensory lesions. The graph shows normal audiometric thresholds and pitch discrimination in an animal having a loss of over 90 per cent of the spiral ganglion cells in the 11 to 16 mm regions.

(B) Cat 2. Normal audiogram and pitch discrimination with 75 to 90 per cent ganglion cell loss in the 11 to 18 mm region.

behaviorally at the 40 db sensation level. The cat was placed in a double grill box and presented with constantly repeated pure tone pulses at a standard frequency. At random time intervals a comparison pulse tone of higher frequency was substituted for every other one of the standard pulses and the cat conditioned to move across the barrier of the cage when these higher frequency pulses were detected. By gradually decreasing the difference in frequency between the

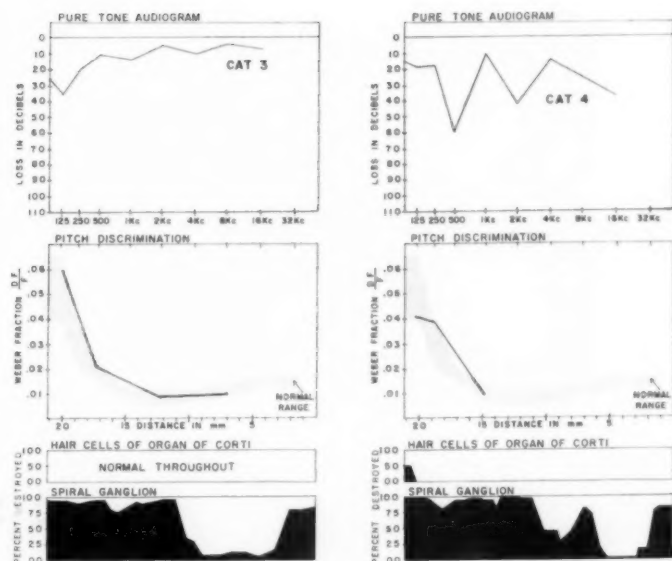


Fig. 2.—(A) Cat 3. Slight hearing loss for the low frequencies and normal pitch discrimination in the presence of a severe loss of ganglion cells in the apical half of the cochlea.

(B) Cat 4. Moderate hearing loss but normal pitch discrimination for low frequencies in an ear with an extensive ganglion cell loss in over half the cochlea.

standard and comparison tones, the limits of the animal's frequency discrimination could be determined. Using this procedure, the relative discrimination thresholds (i.e., the ratio of the just noticeable difference in frequency to the standard frequency) were obtained for each cat at several frequencies. These thresholds were then compared with thresholds which had been determined previously on eight normal cats.¹

After determining the discrimination thresholds, the animals were sacrificed by intravital perfusion and the temporal bones serially sectioned, stained and mounted by routine methods. The cochleas

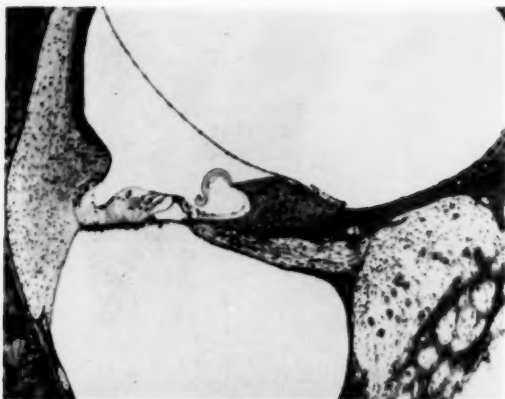


Fig. 3.—Photomicrograph from the 14 mm region of the cochlea of Cat 4, showing a normal organ of Corti and a loss of about 90 per cent of the spiral ganglion cells following partial section of the cochlear nerve. The animal was sacrificed by arterial perfusion with Heidenhain-Susa solution 9 months after operation. Function and pathology charted in Figure 2B.

were graphically reconstructed and plots made to show the magnitude of the sensory and neural lesions.

RESULTS

A. Cochlear Nerve Lesions. Cat 1. This cat, which survived 8 months after operation, had a normal audiogram and pitch discrimination in the presence of about 90 per cent loss of ganglion cells in the 12 to 16 mm region (Fig. 1A).

Cat 2. This cat survived 5 months after operation and had a normal audiogram and pitch discrimination with 75 to 90 per cent ganglion cell loss in the 11 to 18 mm regions and a smaller loss at the extreme basal end (Fig. 1B).

Cat 3. This cat survived 5 months after operation and showed a hearing loss of 30 db for the very low frequencies and less for other frequencies in the presence of 90 to 95 per cent ganglion cell loss

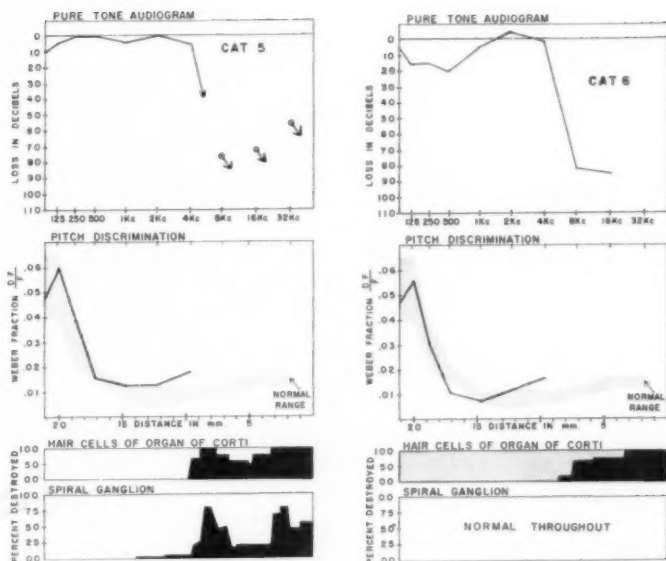


Fig. 4.—(A) Cat 5. This ear was exposed to a 7,700 cps at an intensity of 143 db (re .0002 dynes/cm²) for 5 minutes. There is a basal cochlear lesion which has created a high frequency hearing loss but pitch discrimination for frequencies up to 4 kc is normal.

(B) Cat 6. A 7,700 cps tone was delivered at 143 db for 3 minutes. The experimental results are similar to Cat 5, in spite of a mild diffuse atrophy of the organ of Corti (indicated by stippling in the cochlear chart).

throughout the upper half of the cochlea. There was also a smaller loss at the extreme basal end (Fig. 2A).

Cat 4. This cat survived 9 months after operation and had a hearing loss for the different frequencies varying from 10 to 60 db but normal pitch discrimination for the frequencies tested (Fig. 2B). It sustained a ganglion cell loss slightly greater than Cat 3 (see Fig. 3).

B. Sensory Cell Lesions. Cat 5. This animal was exposed to a 7,700 cps tone at 143 db for 5 minutes, and sacrificed 6 months later. Absolute thresholds and pitch discrimination were normal for fre-

TABLE I
FREQUENCY, INTENSITY, AND DURATION OF
OVERSTIMULATING TONES

CAT	FREQUENCY	INTENSITY	DURATION
5	7,700 cps	143 db*	5 - min.
6	7,700 cps	143 db	3 - min.
7	7,700 cps	143 db	4 - min.
	7,700 cps (re-exposure)	145 db	5 - min.
8	7,700 cps	140 db	4 - min.
	7,700 cps (re-exposure)	145 db	2 - min.
9	7,700 cps	144 db	10 - min.
	11,900 cps	132 db	10 - min.
	15,700 cps	131 db	10 - min.
	18,000 cps	118 db	10 - min.
	25,600 cps	116 db	10 - min.

* re 0.0002 dynes/cm²

quencies up to and including 4,000 cps and an abrupt profound hearing loss existed for frequencies above 4,000 cps. Examination revealed a severe loss of hair cells and a moderate loss of ganglion cells in the basal 10 mm of the cochlea, corresponding to the areas of maximum importance for the depressed high frequencies (Fig. 4A).

Cat 6. This animal was exposed to a 7,700 cps tone at 143 db for 3 minutes, and sacrifice 4 months later. There was a mild hearing loss (15 to 20 db) for the low frequencies and a profound loss for frequencies above 4,000 cps. Pitch discrimination was normal. Examination showed a severe hair cell loss in the basal 8 mm of the cochlea. In addition, there was a mild diffuse atrophic change in the membranous labyrinth. This consisted of slight shrinking of the organ of Corti and tectorial membrane and of the vestibular sense organs (Fig. 4B).

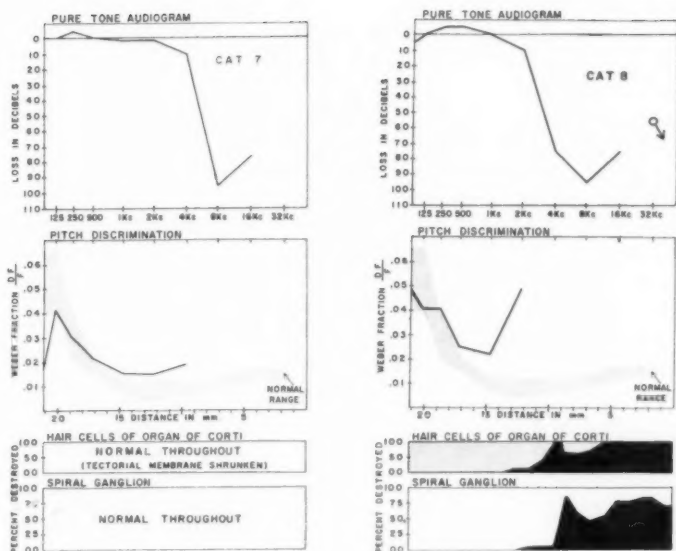


Fig. 5.—(A) Cat 7. Stimulation to a 7,700 cps tone was given for 4 minutes at 143 db and later for 5 minutes at 145 db. The hair cell and ganglion cell populations were normal. The tectorial membrane was atrophied. The audiogram and pitch discrimination are similar to Cats 5 and 6 (Fig. 4).

(B) Cat 8. Stimulation to 7,700 cps was given for 4 minutes at 140 db and 4 weeks later for 2 minutes at 145 db. The increase in pitch discrimination thresholds for the 2 kc frequency cannot be readily explained as the inner ear changes were not different from those of some other animals. The stippling in the cochlear chart represents an atrophic change in the organ of Corti (Fig. 6B).

Cat 7. This animal's experimental ear was exposed to a 7,700 cps tone for 4 minutes at 143 db. This was repeated for 5 minutes at 145 db four weeks later. The animal was sacrificed after 5 months. Absolute thresholds and discrimination was normal for all frequencies up to and including 4,000 cps, with a profound hearing loss for frequencies higher than 4,000 cps. The populations of hair cells and ganglion cells were normal throughout. There was shrinking of the tectorial membrane throughout the cochlea and of the otolithic mem-

brane of the saccule. This shrinking of the tectorial membrane existed in the presence of an organ of Corti which appeared normal in other respects (Fig. 5A). In the opposite ear, which had been rendered nonfunctional by a previous surgical procedure, the tectorial membrane was well preserved and the apex appeared normal. As the two ears had been prepared histologically in continuity, we believe the atrophic changes in the tectorial membrane of the experimental ear existed before death and were due to overstimulation. Also, we believe the hearing tests are valid in that they were performed independently by two operators. Animals being tested concurrently in other experiments manifested normal high frequency hearing, which minimizes the possibility of equipment failure. There were no changes in this ear which could be correlated spatially with the depressed thresholds. We believe that the hearing losses are due to structural alterations in the organ of Corti which interfere with excitation phenomena but are not detectable by light microscopy.

Cat 8. This animal was exposed to 7,700 cps at the sound pressure level of 140 db for 4 minutes. The stimulation was repeated in 4 weeks at 145 db for 4 minutes, and the animal was sacrificed 8 months later. Absolute thresholds were normal up to and including 2,000 cps with an abrupt severe hearing loss for higher frequencies. Pitch discrimination was normal for low frequencies but significantly decreased for 2,000 cps (Fig. 5A). Examination revealed a severe loss of hair cells and ganglion cells in the basal 9 mm of the cochlea corresponding to the spatial distribution of the frequencies with depressed thresholds. In addition, there were diffuse atrophic changes (shrinking) of the organ of Corti, including the tectorial membrane, and of the vestibular sense organs (see Fig. 6A and 6B). There was, nevertheless, a normal population of hair cells and ganglion cells in the apical half of the cochlea and in the utricle and cristae. There was a large rupture and collapse of the saccular wall with degeneration of part of its macula.

Cat 9. This animal was exposed during one session to 5 different frequencies ranging from 7,700 to 25,600 cps as shown in Table I. The animal was sacrificed 6 months later. The audiogram showed a hearing loss of 25 db for the 62.5 and 125 cps frequencies, with the loss becoming progressively worse for higher frequencies reaching a level of 95 db for 4,000 cps and no hearing for higher frequencies at the maximum test intensities.

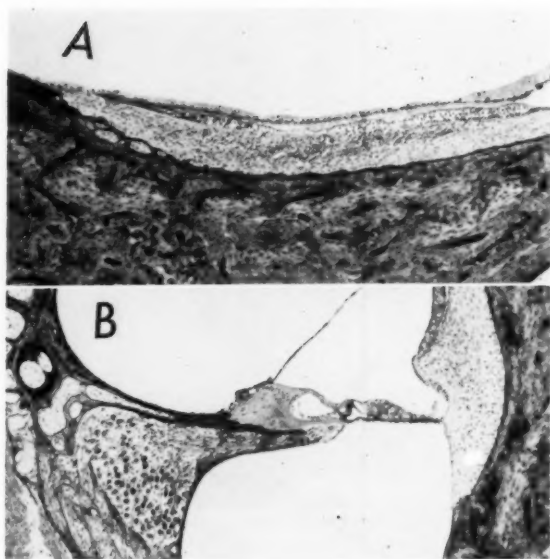


Fig. 6.—(A) Saccule of Cat 8 showing collapse of the saccular wall (after rupture) onto the macula with partial destruction of the sensory epithelium.

(B) Organ of Corti from the 18 mm region of Cat 8 showing atrophy (shrinking) of the organ of Corti and tectorial membrane. The hair cells are present and hearing is normal for frequencies affecting this region of the cochlea. The stria vascularis, spiral ligament, limbus and spiral ganglion are normal.

Discrimination was normal for the frequencies tested (62.5, 125, 250, 500, 1,000 cps). Examination revealed a total loss of hair cells in the basal 11 mm of the cochlea and then progressively less loss to reach normal at 17.5 mm. Ganglion cell loss existed only in the basal half of the cochlea (Fig. 7). It is of interest that the inner ear of this animal with the most severe sensory cell deficit and hearing loss fails to have the atrophic (shrinking) alterations of the sense organs or tectorial membrane (Fig. 8A and 8B) in varying degrees in three other ears (Cats 6, 7 and 8).

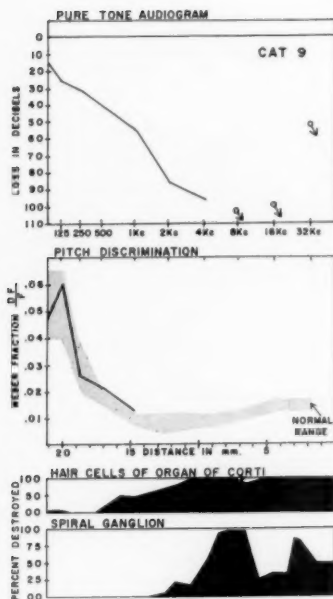


Fig. 7.—Cat 9. This animal was exposed to a series of frequencies ranging from 7,700 to 25,600 cps (see Table I). The severe hearing loss is compatible with the magnitude of the sensory lesion. Pitch discrimination is normal for low tones, in spite of functional loss of the basal half of the cochlea (see photomicrographs in Figure 8).

COMMENT

Analysis of these data of the nerve lesion animals shows that in no case was a complete regional loss of ganglion cells created. Some innervation always was present, although in some areas less than 5 per cent of the innervation remained. The data indicate that for the low and middle frequency range, absolute thresholds are normal when only 5 to 10 per cent of the innervation remains so long as the area of involvement is only a few millimeters long, whereas with broader areas of a severe loss of innervation the thresholds are elevated. It is known that many nerve fibers to the outer hair cells travel several millimeters within the organ of Corti, either towards the apical or towards the basal end, and innervate many hair cells along the way.

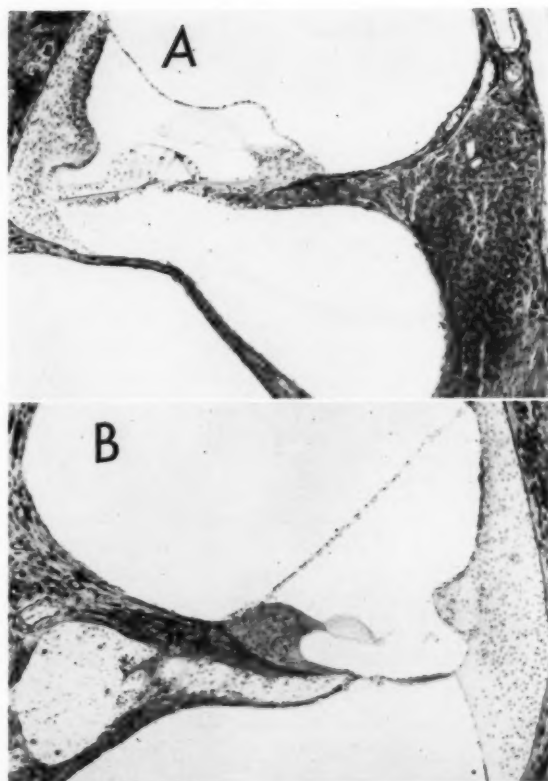


Fig. 8.—(A) Cat 9. Normal organ of Corti in the 18 mm region.
 (B) Cat 9. Complete loss of the organ of Corti and spiral ganglion and atrophy of the stria vascularis in the 8 mm region.

This anatomical fact suggests, therefore, that in the case of severe nerve lesion involving but a small region of the cochlea in an animal with normal auditory thresholds, part of the critical innervation is supplied by distant ganglion cells whose fibers are overlapping into the area of the lesion. On the other hand, when the loss of ganglion cells involves a greater part of the cochlea, the contribution from

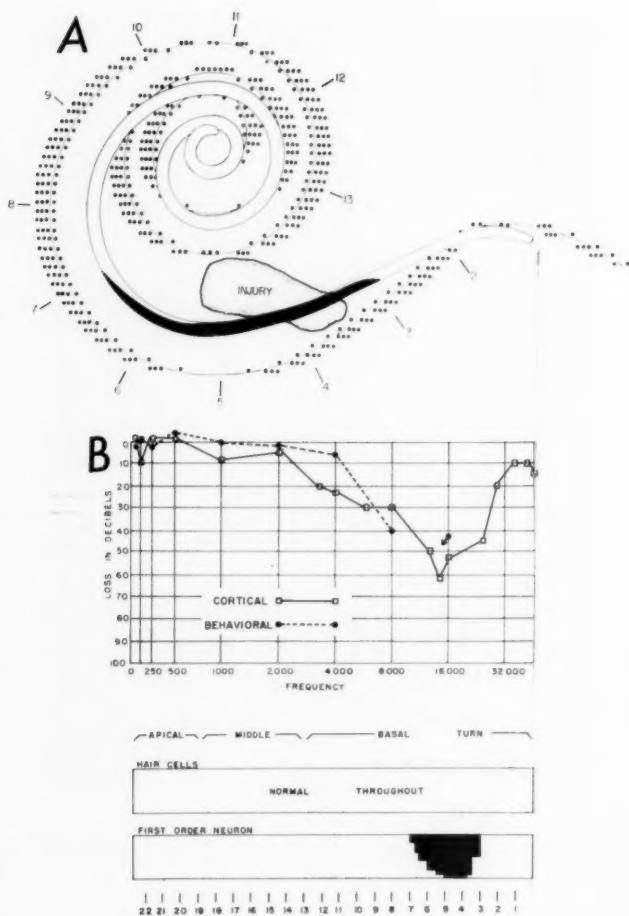


Fig. 9.—(A) Spiral graphic reconstruction of the organ of Corti and spiral ganglion of a cat suffering a restricted loss of innervation (black fillings in spiral channel) to the 3 to 7 mm region as the result of a fine needle puncture into the osseous spiral lamina. The hair cell population is normal.

(B) Cortical² and behavioral audiograms and cochlear chart for the same animal showing that a restricted area of denervation in the basal turn does create a hearing loss.

overlapping fibers is diminished and the deficit of fibers more easily exceeds a critical minimum. This "overlapping innervation" concept does not apply to high frequencies however, for it has been shown in a previous experiment that a small region of complete denervation in the basal turn does create a threshold loss (Fig. 9).²

Pitch discrimination determinations were made at intensities well above the threshold of sensation so that greater areas of the cochlea were brought into activity. It is known that for each frequency there is a region of maximum excitation along the cochlear duct. With increasing stimulus intensity the area of maximum activity shifts very little, if at all, whereas the field of excitation spreads, particularly toward the basal end. It has been estimated that the spread of the effective field of excitation for low frequencies was about 0.2 mm for each db increase in intensity. These values were 0.14 mm for midrange frequencies, 0.11 mm for high frequencies, and 0.056 mm for the very high frequencies.⁸ Thus, for cats 1 and 2 with normal absolute thresholds, since discrimination was tested 40 db above the threshold, the effective neural activity for low frequency tones probably occurred within an 8 mm region (from about the 12 to the 20 mm area). For cats 2 and 3 with moderate hearing losses, on the other hand, the tests were performed about 60 db above normal thresholds and the excitation fields were probably about 12 mm long (from about the 8 to 20 mm area). Thus, even in the presence of a severe neural deficit, discrimination tests on these ears bring into activity a great many neural units.

As we were not able to completely denervate the apical regions it was still possible for modal (peaked) excitation fields to occur in response to low frequencies. We believe that as pitch changes there is a spatial shifting of the modal excitation field which is easily detected so long as some small critical number of neural units remain spatially dispersed along the longitudinal dimension of the sense organ.

Pitch discrimination of the overstimulation ears, with one exception, was essentially normal. It would appear, therefore, that pitch discrimination as it was measured for the low and medium frequencies at the 40 db sensation level was not affected greatly, if at all, by loss of the basal turn. It appears, therefore, that neural coding for pitch discrimination must lie in the regions of maximum excitation. If

additional periodicity cues for pitch do arise in the basal turn, they certainly do not appear to be particularly important since their loss is not reflected in our data. The manner of coding for pitch is not known, of course, but a widely accepted concept is that it is related to the spatial location of the point of maximum amplitude on the basilar membrane. Because of the momentary phase differences at different points along the upper end of the cochlea of the traveling wave, we doubt that coding is concerned simply with the impulse frequency in the fibers.

The poor pitch discrimination exhibited by Cat 9 at the 2 kc frequency is puzzling. Possibly the atrophic conditions of the organ of Corti caused this decrement in performance. However, by our methods of examination, the histopathological changes in the cochlea of this ear do not differ significantly from those in some of the ears having normal discrimination. Because of the few ears involved in this study it seems futile to speculate seriously on the causes for this single discrimination loss.

Examination of the atrophic changes existing in the 3 ears seems to indicate that these alterations may involve part or all of the histological structures of the cochlea and vestibular labyrinth. The stria vascularis, spiral ligament and limbus are normal in these ears. The tectorial membrane in itself may be shrunken (flat and dense) with a normal underlying organ of Corti or the organ of Corti may also be shrunken. In the latter case, Reissner's membrane may be displaced somewhat into the cochlear duct. The histological picture is similar to Wittmaack's "hypotonic degeneration." At first we thought that this reaction might result from saccular rupture because the saccules were ruptured in all 3 ears showing atrophic changes. However, controlled saccular ruptures have been created in chronic experiments in cats without producing atrophic changes in the cochlea.³ McCabe and Lawrence have described saccular ruptures in guinea pigs following intense auditory stimulation, and we also have seen this happen in cats as a result of head blows and stapes fractures.^{4,9,10} In none of these animals, however, has there been atrophy of the tectorial membrane and organ of Corti. Atrophic alterations of this nature have not occurred in other ears undergoing similar arterial perfusion and histological preparation in concurrently executed experiments in our laboratory. A surprising feature of the

condition is that it is compatible with normal absolute pure tone thresholds and discrimination.

SUMMARY

Absolute pure tone thresholds and frequency discrimination thresholds were determined on a series of 9 cats, 4 with surgically created nerve lesions and 5 with basal turn receptor cell lesions created by overstimulation.

It was found that over 90 per cent of the nerve fibers could be lost to a region of the cochlea measuring 5 to 6 mm in length without affecting the pure tone thresholds. When the longitudinal dimension of the lesion was somewhat more extensive (for example, 11 mm long), hearing losses did result. One possible explanation for this is that the overlapping innervation from nerve fibers traveling along the organ of Corti for limited distances was capable of maintaining normal thresholds, as long as the extent of the lesion did not exceed the length of the spiral fibers.

Pitch discrimination was found to be normal, even in the presence of severe neural deficits. It was not possible to completely denervate any particular region of the cochlea so that at the 40 db sensation level the pitch discrimination tests brought into activity a great many neural units. Thus, it appears that in these partly denervated ears it was still possible for modal (peaked) excitation fields to occur in response to pure tone stimuli. As pitch changes, the spatial shifting of the modal excitation field apparently can be detected, so long as some small critical number of neural units remains spatially dispersed along the longitudinal dimension of the sense organ.

High frequency overstimulation caused severe receptor cell destruction of the basal turn of the cochlea with the expected high frequency hearing losses. No changes were noted in discrimination (with one exception), suggesting that pitch cues for low frequencies are being coded in the apical regions of the cochlea, and not from periodicity cues arising in the basal turn. In 3 of the 5 animals in which lesions were created by overstimulation there were atrophic (shrinking) alterations in remote areas of the cochlea and in the vestibular labyrinth. The cause of these atrophic changes is not

evident but they are almost certainly due to the high intensity high frequency stimulation and it appears that they are compatible with normal auditory function.

WEST GRAND BLVD. AT HAMILTON

The author is greatly indebted to Dr. Harold F. Schuknecht for his assistance and advice in planning and carrying out this study. He created the partial nerve sections and assisted, as well as advised, on the evaluation of the histopathological data. In addition, Dr. Schuknecht discussed with the author at length the theoretical interpretation of the data.

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ACOUSTIC MEASUREMENT OF THE
MIDDLE EAR FUNCTION

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As a result of the fenestration and mobilization operations, the interest in the middle ear function has grown considerably. Of particular interest are the pre-operative diagnostic examination and the postoperative check-ups. The principal tests can be divided into two categories: the otoscopic observation, and the audiometric tests. The otoscopic observation has the advantage of independence of the cochlear and retrocochlear portions of the auditory mechanism and is free from the influence of the psychological attitude of the patient. These advantages are offset to a certain extent by the qualitative nature of the observation which depends heavily on the subjective judgment of the examiner. Also, the tests of eardrum mobility involve extremely large amplitudes of motion, which may not reflect accurately the function of the middle ear involved in the hearing process. The audiometric tests are largely quantitative and are reasonably independent of the examiner's subjectivism. However, they depend strongly on the patient's subjective decisions and involve the totality of the auditory system.

The method of examination suggested in this paper is quantitative, objective, and its results are determined exclusively by the sound transmitting system of the ear, i.e. by the middle ear and, to a lesser extent, by the cochlea. The amplitude and the frequency of vibration involved are those normally encountered during the process of hearing.

The method is based on acoustic measurement, and before it can be discussed, it appears necessary to describe in a few words the sound

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propagation in the outer portions of the ear, and to introduce certain acoustic concepts and definitions.

When an acoustic wave enters the external auditory meatus, it progresses in it until it reaches the eardrum. There, part of its energy is reflected and the remaining part produces a vibration of the eardrum. This vibration is transmitted to the inner ear through the intermediary of the ossicular chain. Under normal conditions, only a small portion of the acoustic energy transmitted to the eardrum is absorbed by the middle ear. Most of the energy enters the cochlea; a fact that contributes to the high sensitivity of the auditory system.

The reflected energy forms a wave that is propagated from the eardrum outwards. Its frequency is identical to that of the incident wave, its amplitude and phase depend on the acoustic conditions encountered at the eardrum. These conditions are controlled by the properties of the eardrum, the ossicular chain, the middle ear muscles and ligaments, the two cochlear windows, the middle ear cavity and the interconnected pneumatic cells. To a lesser extent, they are controlled by the mechanical properties of the inner ear. Thus, the wave reflected at the eardrum carries information concerning the state of the middle ear. This information is somewhat similar to that carried by a light wave reflected from a translucent object. Due to the nature of our sense organs, it is usually possible to extract more information from light waves than from sound waves. Sometimes the reverse is true, however. In testing the middle ear function, sound may be more informative.

The acoustic energy carried in a sound wave may be determined indirectly by measuring the so-called sound pressure. The sound pressure is nothing else than a variation in the atmospheric pressure, which is produced by a vibrating body, for instance, a tuning fork or an earphone. The sound pressure measured in the ear canal results from both the incident and the reflected waves. When the incident wave is known, its sound pressure can be eliminated from the total and the sound pressure of the reflected wave obtained.

It should be plausible that the energy of the reflected wave is maximum when the middle ear mechanism is either so stiff or so heavy that no motion can be imparted to it by the air particles, and

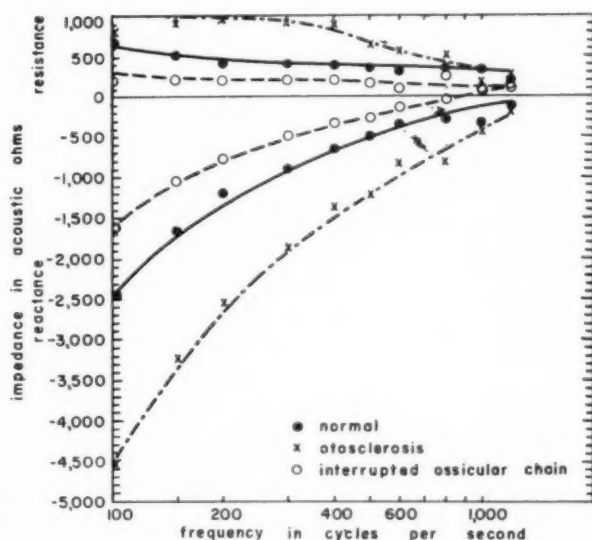


Fig. 1.—Average reactance curves determined at the eardrum. Values indicated by closed circles were obtained on normal ears, those indicated by crosses—on otosclerotic ears, and those indicated by open circles on ears with a severed incudo-stapedial joint.

consequently, no energy transmitted. The same effect may result from extreme viscosity which produces a strong internal friction. When the system is compliant and light and has little internal friction, it can move easily under the effect of the force of sound pressure. In general, the resistivity to motion is called in acoustics "impedance." The impedance has three definitions. The mechanical impedance of a system is defined as a ratio between the force and the velocity of motion generated by the force. The specific impedance is defined as a ratio of the sound pressure and of the velocity of displacement it produces. The acoustic impedance is identified as a quotient of the sound pressure and of the rate of volume displacement, abbreviated by "volume velocity." When, for instance, a pressure is applied to the eardrum each portion of the eardrum is displaced by a certain distance. The displacement of the eardrum as a whole amounts to a

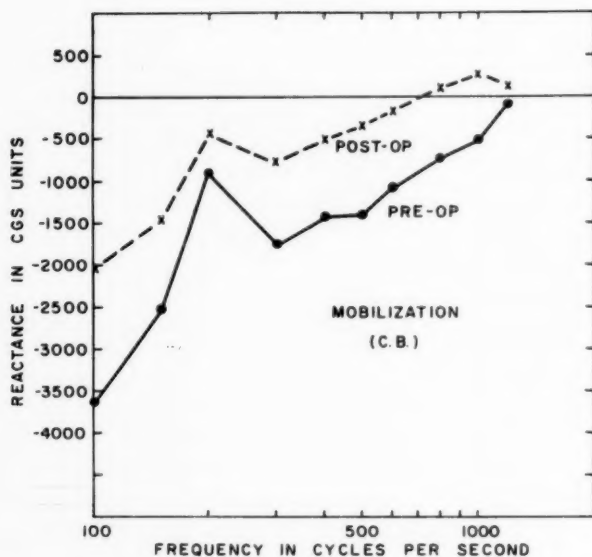


Fig. 2.—Individual reactance curves of an otosclerotic patient taken before and several weeks after mobilization.

certain volume of air. The rate at which this displacement takes place is called volume velocity.

It is acoustically convenient to express the eardrum mobility in terms of the acoustic impedance.

The acoustic impedance has three components as already mentioned. They are proportional to stiffness, mass, and resistance, respectively. The concept of stiffness should be clear; the mass is proportional to the weight of an object; the resistance depends on viscosity or friction. The effect of stiffness is greatest at low sound frequencies, that of mass at high frequencies; the effect of friction is frequency independent. It is worth noting that the effects of stiffness and mass may cancel each other, and that it is always possible to find at least one sound frequency at which the cancellation takes place. Such a

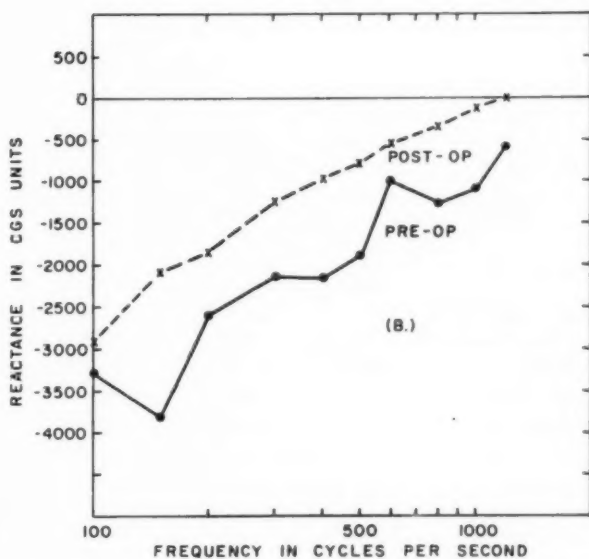


Fig. 3.—Same as Figure 2 for another patient.

frequency is called resonance frequency. The lowest resonance frequency of the middle ear mechanism seems to lie around 1,000 cps.

It is sufficient to measure the ratio of the reflected and the incident waves in order to determine the acoustic impedance at the eardrum. This impedance expresses the acoustic properties of the middle ear mechanism as a whole and is affected by pathological changes. For instance, stapes ankylosis or adhesions increase the stiffness and the resistance. A disturbance in the position of the ossicles increases the mass component. An interrupted incudo stapedial joint reduces both the stiffness and the resistance. This is due to the fact that a considerable portion of the stiffness component is contributed by the stiffness of the oval and the round windows, and most of the resistance component has its origin in the cochlea.

Average impedance components for normal and otosclerotic ears and for ears with an interrupted incudo-stapedial joint are shown in

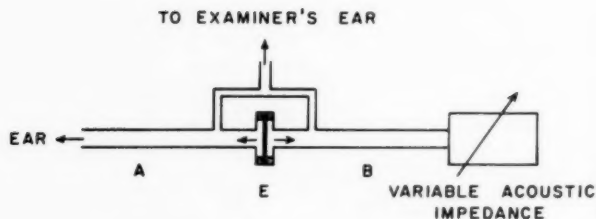


Fig. 4.—Schematic drawing of an acoustic bridge.

Figure 1 as a function of frequency. The stiffness and mass components are not shown separately, but are combined into a resultant component called "reactance." The reactance is negative when stiffness predominates, it is positive when mass has the upper hand. As can be seen in Figure 1, the reactance is negative at low frequencies for the normal as well as for the pathological ears. This means that the middle ear system is stiffness controlled. The stiffness is greatest in the otosclerotic ears and smallest in the ears with the interrupted incudo-stapedial joint. The same is true for the resistance. In normal ears both stiffness and resistance are intermediate.

Figure 1 shows a clear differentiation between normal and two kinds of pathological ears on the basis of acoustic impedance measurements. It is necessary to point out, however, that the data of Figure 1 are averages of several patients. Of clinical importance is the question whether the differentiation can be made on an individual basis. The answer depends on the differences among the averages as well as on the individual deviations from these averages. I feel that no sufficient data are available for the latter consideration, so that no definitive answer can be given at this time. Also, the methods of measurement are still somewhat crude and substantial improvements in this respect can be expected.

Although the dearth of clinical data precludes a definitive statistical evaluation, some results obtained on individual patients appear encouraging. They are illustrated by the next two figures which show reactance curves for two otosclerotic patients before and after mobilization. The difference between the pre- and the postoperative

reactance values is clearly apparent. While before the operation the reactance was considerably larger than in an average normal ear, after the operation it has become nearly normal. Actually, the postoperative reactance of Figure 2 is somewhat below normal at low frequencies and becomes positive above 700 cps. By comparison to the curve of Figure 1 for the interrupted incudo-stapedial joint, this may indicate a slight dislocation of the ossicular chain. The postoperative curve of Figure 3 indicates values somewhat above the norm, which may indicate an incomplete mobilization. However, both postoperative reactance curves are within the range of values obtained on normal ears.

The results of impedance measurements at the eardrum are not always as convincing as those of Figures 2 and 3. Whether this is due to peculiarities of the middle ear system or to imperfections in the method remains to be seen. For the time being, the impedance measurements are not quite ready for routine clinical testing and must be considered an experimental tool.

There are several ways in which the acoustic impedance at the eardrum can be obtained. I shall mention only two examples.

In the first example the sound is generated by an earphone and conducted to the ear canal through a narrow tube. The tube is secured by means of an earplug which fits snugly into the ear canal. Another similar tube mounted in the same earplug leads to a microphone which measures the sound pressure produced in the ear canal. The system may be calibrated on a small cavity with rigid walls. By comparing the sound pressure generated in such a cavity to the sound pressure measured in the ear, the impedance of the ear can be calculated. This impedance is determined by the impedance at the eardrum and the impedance of air enclosed in the ear canal. In order to eliminate the latter, the volume of the ear canal may be determined by filling it with a liquid, for instance, alcohol. Once the volume of air is measured, its impedance can be calculated. The measurements involved in this method are simple, but the calculations needed for the derivation of the impedance values are rather tedious.

In the second example an acoustic bridge is used. The device is shown schematically in Figure 4. It consists of a symmetrical earphone E mounted between two tubes, A and B, of equal diameter and

length. The two tubes are separated by the diaphragm of the earphone, but communicate through the narrow Y-tube bridging the earphone. The top branch of the Y-tube leads to the examiner's ear. Tube A is secured by means of an earplug in the ear canal; tube B is terminated by a variable acoustic impedance. Due to the symmetry of the system, the sound generated by the earphone becomes inaudible to the examiner when the variable impedance terminating tube B is equal to the impedance at the entrance to the ear canal. The measurement is performed by adjusting the variable impedance until the test sound disappears. When the volume of air enclosed in the ear canal is determined prior to the acoustical measurement, an equivalent volume can be inserted between tube B and the variable impedance. In such conditions the impedance values read of the variable impedance are equal to the impedance values at the eardrum. The measurement is direct and no further calculations are necessary.

Several acoustic bridges have been developed in our laboratory, and we hope that they are going to be available commercially before long.

More detailed information on the impedance measurement in the ear can be found in the literature.¹⁻⁵

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XLVII

STAPEDIAL, CAPSULAR AND LABYRINTHINE ANATOMY IN RELATION TO OTOLOGIC SURGERY

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The difficulties encountered in surgery involving the auditory ossicles are mainly dependent upon the following features of anatomy: narrowness of the stapes "niche," or fossula of the vestibular fenestra (Fig. 1, at A) caused by the promontory of the cochlea (Fig. 1, at B), the semicanal for the tensor tympani muscle and the facial canal (Fig. 1, at C); the "cancellous" fabric of the middle layer of the osseous cochlea (Fig. 1, at B); dehiscence of the facial canal (Fig. 1, at C); the excessive fragility of the stapes (Fig. 1, at D) and the pattern of vascular supply in the incus and malleus; the proximity (to the stapedial footplate) of vital parts of the endolymphatic duct-system (Fig. 1, at E); pathological changes (additional to otosclerotic) in the rim of the oval window (Fig. 1, at F); nearness of the fossula of the cochlear fenestra (Fig. 1, at G), the secondary tympanic membrane and of parts of the membranous labyrinth.¹

¹Contributory phases of the investigation have been reported at earlier meetings of the American Otological Society, Inc., published in the Society's Proceedings and in antecedent issues of the ANNALS OF OTOTOLOGY, RHINOLOGY AND LARYNGOLOGY.

Other contributions, relevant to the subject matter of the current paper, appeared in the following issues of the Quarterly Bulletin of Northwestern University Medical School: vol. 26, pp. 344-373, 1952; vol. 28, pp. 17-45, 1954; vol. 30, pp. 235-249, 1956; vol. 30, pp. 331-355, 1956; vol. 32, pp. 157-172, 1958; vol. 33, pp. 44-59, 1959; vol. 33, pp. 110-119, 1959; vol. 34, p. 19-22, 1960.

These articles give detailed information on the development of the stapes and otic capsule and on the early branchial derivation of the auditory ossicles and related structures. At comparable paper on the development of the malleus is in preparation.

From the Department of Anatomy, Northwestern University Medical School, Chicago, Illinois, and the Department of Anatomy, University of Wisconsin, Madison, Wisconsin (Contribution No. 656 from the former).

A study carried out with the continuing aid of the Central Bureau of Research of the American Otological Society and the National Institutes of Health of the United States Public Health Service (Grant No. B 2237.C2).

MATERIALS AND METHODS

This report is based upon a study of otological series and special dissections, upon reconstructions prepared from selected series and upon material generously provided by Dr. Victor Goodhill on malformation of the ossicles and by Dr. Eugene Derlacki on sites of occurrence of otosclerosis.

I. STRUCTURES NEAR VESTIBULAR (OVAL) FENESTRA

In the attempt to widen the field of approach to the stapes, in the fossula of the vestibular fenestra (stapes "niche"), enlargement of the "working space" may entail removal of bone on the promontory and on part of the wall of the facial canal (Fig. 1 at A; Figs. 2 and 3). These preparatory steps in stapedial surgery bring special hazards; even the most careful burring may endanger the sensory mechanisms of the cochlea and jeopardizes the neural supply to the muscles of facial expression.

These statements call for examination of the anatomy of structures situated near the vestibular (oval) window.

a. *Cochlea* (Fig. 1, at B). The vulnerability of the cochlea is due to the developmental peculiarity in its ossification, or, more specifically to the peculiarly spongy character of the middle layer of its trilaminar shell (Fig. 4).

As early as the 21-week stage, in fetal life, the three layers of the cochlear capsule have been formed (Fig. 4a). The innermost layer of endosteal bone, immediately investing the scalae and the cochlear duct is already a complete, but thin, shell for the labyrinthine systems (Fig. 4a at 3). Once formed, this inner lamina retains its fetal character, never to expand or undergo appreciable alteration in histological texture. Cartilage predominates in portions of the middle layer (Fig. 4a, at 2) where, at a slightly earlier stage, it was continuous with that of the *fissula ante fenestram* (Fig. 4a, at arrow). The outer layer (Fig. 4a, at 1) is still thin.

Within a two-week period, the outermost layer of periosteal bone (covered by the mucous membrane of the tympanic cavity) has thickened appreciably (Fig. 4b). As a result of peripheral increment,

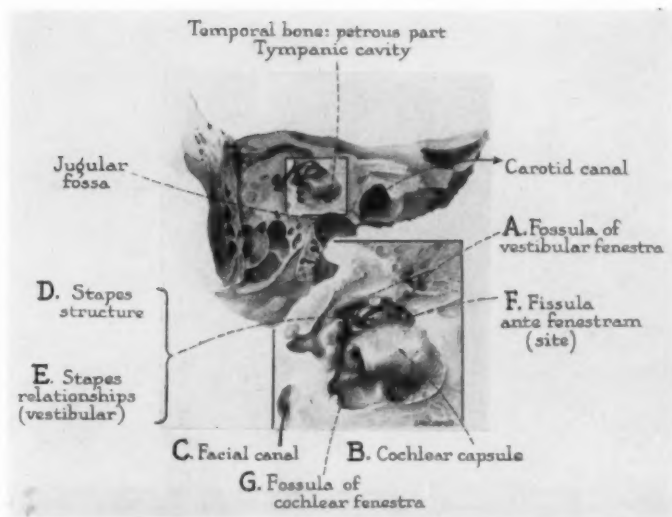


Fig. 1.—Specimen demonstrating the structures (lettered A to G) on the medial wall of the tympanic cavity which are discussed in the present article.

it will finally imbed the capsule in the *pars petrosa* of the temporal bone. The middle layer is made up of scattered "cartilage islands" (intrachondrial bone) lodged in considerable marrow (Fig. 4*b*, at 2).

The middle layer in the late fetus still consists largely of marrow tissue (Fig. 4*c*, at 2). Although endochondral bone is being gradually applied to the intrachondrial spicules, marrow is still considerable in amount. The outer layer has thickened. The inner lamina has received an application of bone from the middle layer. It has not undergone intrinsic thickening. During early infancy, marrow is gradually replaced through increase in the formation of endochondral bone (Fig. 4*d*). Typically, this change results in production of the petrous structure of the capsule.

In some instances the "cancellous" character of the middle layer persists, even into adulthood (Fig. 4*d*, at 2). Consequently, an instrument (for example, a burr) encounters a spongy stratum, deep

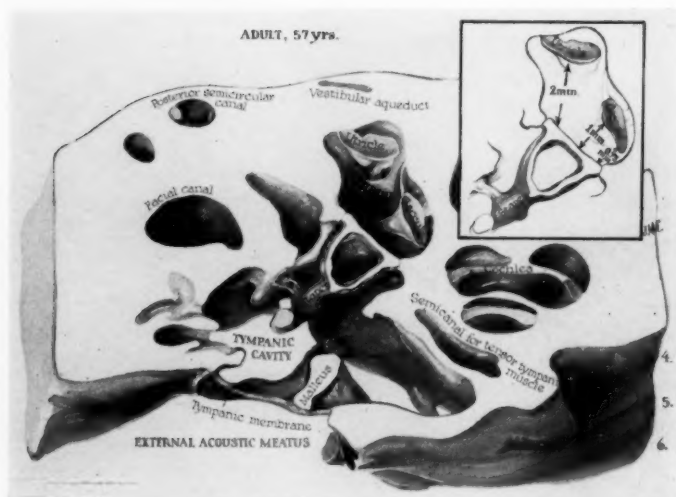


Fig. 2.—Reconstruction of the ear (shown also in Figure 3) divided at a level (segment 3) which demonstrates the following features: the degree to which the canal for the facial nerve and the semicanal for the tensor tympani muscle serve to deepen the stapes "niche" (fossula of the vestibular fenestra); the relation of the footplate (base) of the stapes to the utricular and saccular parts of the membranous labyrinth; the pyramidal eminence and the tendon of the stapedial muscle (at *). Inset: distances between the stapedial base and the utricle and saccule. Specimen, adult, 57 years old. X 5. Original reconstruction X 20.

to which there remains nothing more substantial than the thin inner layer to protect the labyrinthine scalae and duct of the cochlea from an unguarded thrust.

b. *Facial Canal* (Fig. 1, at C). Dehiscence of the facial canal is a developmental defect which is receiving increasing attention in otological reports.² It may be regarded as a classical example of a congenital failure that comes to assume first-rank importance in end-aural surgery performed on the adult (because incompleteness in the

² An informative paper on this subject was presented by Dr. Edmund P. Fowler, Jr., at the meeting of the Eastern Section of the Triological Society, Boston, Massachusetts, January 6, 1961.

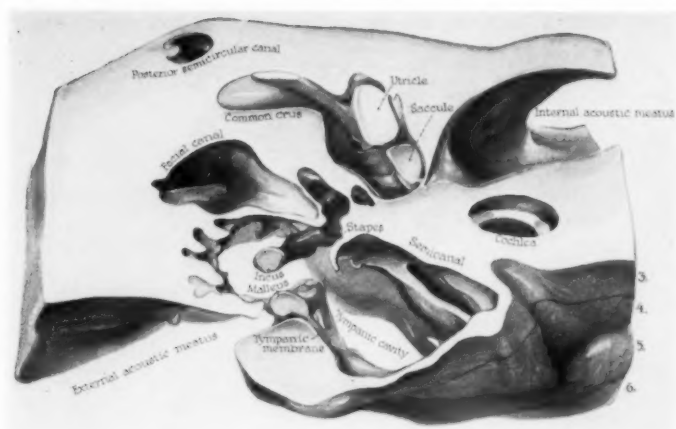


Fig. 3.—Reconstruction opened at more cranial level (segment 2), showing more effectively the anatomical structures which contribute to the depth of the stapes "niche."

wall of the canal leaves the nerve exposed in submucosal tissue, directly in the path of approach to the stapes).

Viewed in the light of its developmental history, incompleteness of the facial canal, rather than maturity in its formation, would be the expected outcome of the complex series of steps through which the constituent portions must pass.

In the fetus of 10 week Reichert's cartilage (second branchial arch) is an histologically unmodified projection from the lateral wall of the canalicular division of the otic capsule (Fig. 5*a*). Being incurved, the projection forms approximately two-thirds of a wall for a primitive facial "canal."

Within less than a three-month period (in the fetus of 21 weeks), although the process of ossification has involved a considerable portion of the otic capsule, cartilage persists in the canalicular division, the capsular wall of the facial canal and Reichert's cartilage (Fig. 5*b*).

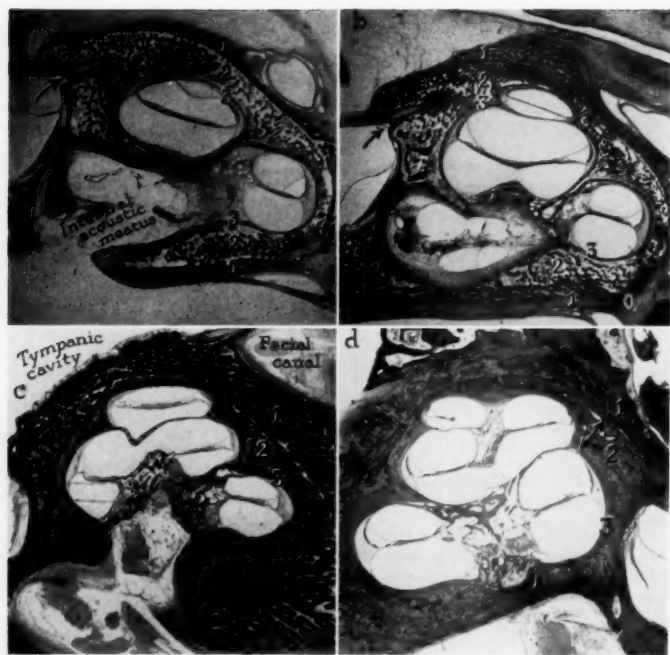


Fig. 4.—Transverse sections, demonstrating major stages in the development of the trilaminar wall of the cochlea. *a*, fetus, 21 weeks (183 mm); *b*, fetus, 23 weeks (210 mm); *c*, fetus, 31 weeks (280 mm); *d*, adult, 46 years. X 6. The layers of capsular bone are numbered as follows: 1, outer, periosteal; 2, middle, intrachondrial and endochonchral; 3, inner, endosteal. In *a* cartilage is indicated by *; in *a* and *b* the arrow points to the vestibular orifice of the fissula ante fenestram; in *d* the arrow crosses the middle layer.

The incomplete channel contains the facial nerve and stapedial muscle, both lodged in vascular mesenchymal tissue.

In a fetus three weeks older (24 weeks), the process of ossification has advanced to convert the capsular (medial) wall of the facial canal into bone (Fig. 5*c*). The bone is of two types; namely, intrachondrial in the depths of the canal, and membrane at the free margins (where the wall is still incomplete). On the tympanic (lateral)



Fig. 5.—Transverse sections selected to show the chief steps in development of the facial canal. *a*, fetus of 10 weeks (50 mm); *b*, fetus of 21 weeks (183 mm); *c*, 24 weeks (215); *d*, 34 weeks (310 mm); *e*, fetus at term; *f*, infant, 6 months. X 9. In *a* the arrow passes through the tympanomeningeal hiatus; in *c* through *f*, the asterisks indicate bays of the expanding tympanic cavity; in *d* the arrow points to the developing membrane bone; in *e* the arrow indicates the line of junction of the ossifying and the as yet unmodified parts of Reichert's (hyoid) arch.

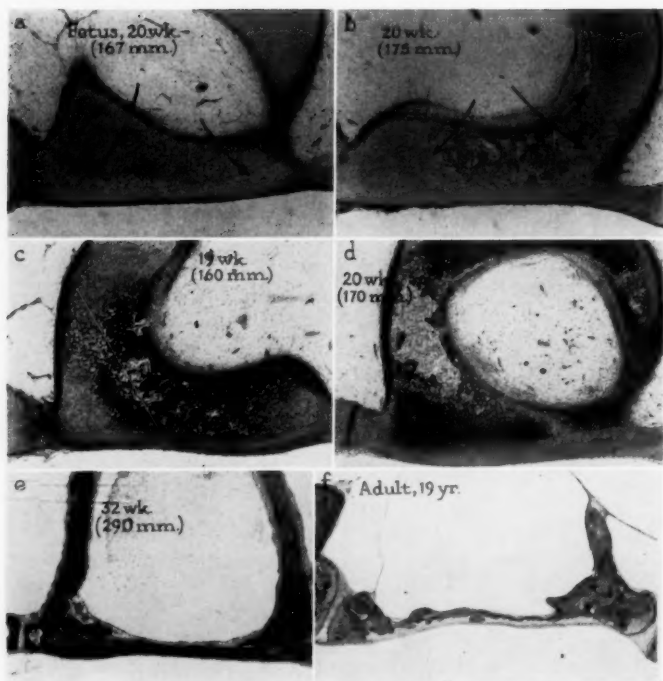


Fig. 6.—Transverse sections from otological series recording the succession of changes in the stapes through five fetal stages, and outcome, in the adult, of the processes pictured. *a* to *d*, X 24; *e* and *f*, X 13. In *a* the arrows pass through cartilage which is undergoing modification preparatory to conversion into bone; in *b* the arrows indicate the depth of the ossification center (beyond the cartilage will persist as the *lamina stapedis*).

surface of the capsule, persistent cartilage is still continuous with that of the branchia arch (Reichert's cartilage). Expansion of the tympanic cavity has carried the mucous membrane medialward to the otic capsule (Fig. 5*c*, at *).

In the course of development through a 10-week period (in a fetus of 34 weeks), while Reichert's bar remains cartilaginous, a new element has appeared: membrane bone now contributes to produc-

tion of a complete wall for the canal (Fig. 5*d*, at arrow). The expanding tympanic cavity produces irregular bays which now begin to intervene between the newly-formed bone and Reichert's cartilage (in Fig. 5*d*, summit of one such bay is indicated by *).

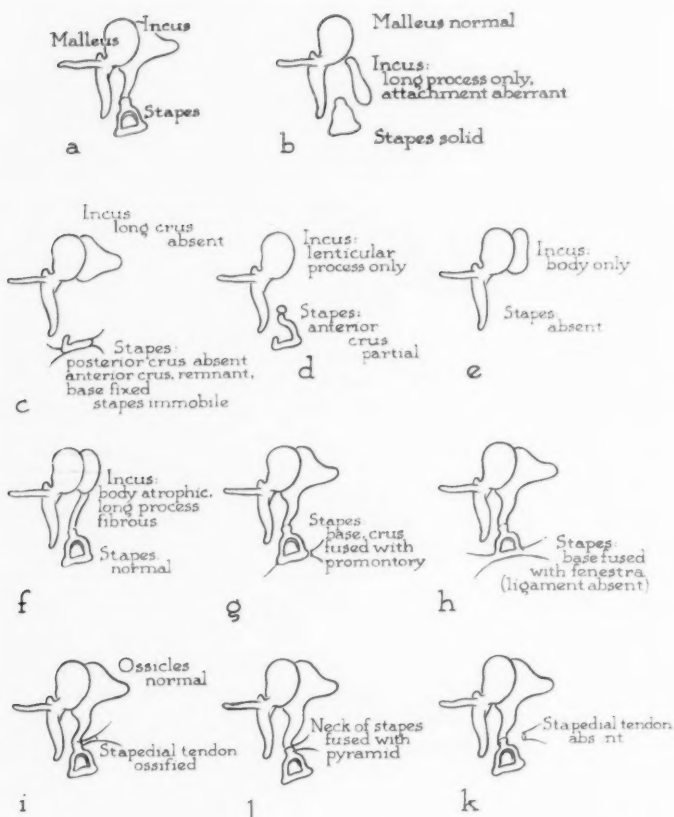
In the fetus at term, although Reichert's cartilage remains in part chondral in the area of cranial attachment to the otic capsule, it is undergoing ossification (Fig. 5*e*, at the tip of the arrow). Membrane bone, in producing an outer (tympanic) wall for the facial canal, now separates the contents of the canal from Reichert's cartilage. An offset of the tympanic cavity intervenes (Fig. 5*e*, at *) between the facial canal and the cartilaginous branchial arch. Similar membrane-lined bays occur along the tympanic wall of the otic capsule.

In the young infant, the cartilage of Reichert's bar has given way to bone. However, the interrelationship of structures and spaces, established in the 24-week stage, remains essentially unchanged (Fig. 5*f*). In succession from superficial to deep, these are: the tympanic cavity; Reichert's cartilage; a bay of the tympanic cavity (Fig. 5*f*, at *); the facial canal containing the nerve, blood vessels and stapedial muscle. At this level, the muscle, in approaching the pyramid, courses through a partially segregated channel.

Even when it is complete, the wall of the facial canal is regularly thin and, therefore, easily broken. It has been established that, because bone-formation progresses cranialward, the facial canal may still be unclosed in its upper reaches in the late fetus. In some cases, other portions of the wall remain incomplete, even in the adult—a circumstance perhaps dependent upon the complexities of a four-part derivation.

In this as well as in all comparable instances, the surgeon is forewarned of technical danger when he is aware of the normal course of morphogenesis and of the possible failure in the faltering steps that should bring an organ or an organ-system to full maturity. Surely, for no other surgical specialty is such foreknowledge as important as it is to the otologic surgeon.²

c. *Auditory Ossicles* (Fig. 1, at D). STAPES.—The most striking feature of the stapes is its excessive thinness.



From the Otological Service
of Victor Goodhill, M.D.

Fig. 7.—Anomalies of the auditory ossicles; drawings prepared from sketches generously provided by Dr. Victor Goodhill, Medical Center, University of California.

Fragility of the stapes in the adult ear (Fig. 6f) is the direct outcome of the developmental steps through which the ossicle passes (Figs. 6a to 6e).

While undergoing rapid increase in size, the ring-shaped cartilaginous "stapes" of the early embryo attains the form of a stirrup. Ossification is predicted by a change in the consistency of the cartilage on the tympanic aspect of the base (Fig. 6a, inward to the points of the arrows). Erosion and calcification of cartilage are well advanced in other specimens of similar age (Figs. 6b to 6d).

In a second example of the 20-week stage bone-formation (from the solitary ossification center) involves the base of the stapes (Fig. 6b, again, to points of the arrows) to the depth indicated in the preceding stage.

Periosteal bone soon surrounds the crura, extending across the base and into the neck of the stapes. During the same period, the bone which forms the obturator wall is being resorbed circumferentially (Figs. 6c and 6d).

Near term, in the 32-week fetus, the entire obturator portion of head, crura and base has been removed (Fig. 6e). Endosteal tissue, corresponding to the cancellous architecture of a typical long bone, formed sparsely, quickly disappears. Concurrently with its resorption, marrow is removed and replaced by mucous membrane of the expanding tympanic cavity.

As a result of these changes, the stapes of the fetus at term is virtually indistinguishable from that of the adult (Fig. 6f).

This means that the stapes, even before birth, has been converted into the fragile ossicle which is invariably encountered in the adult. The stapedial base (footplate) of the mature ossicle (in a typical instances) is a thin, oval plate, whose greater and lesser diameter may measure no more than 2.75 mm and 2.0 mm, respectively, and whose thickness may vary from 0.0425 mm (at the center) to 0.5 mm (measured at either extremity where the crus is implanted into the footplate).

Two additional structural features are worthy of practical consideration: one has to do with the persistence of embryonic cartilage

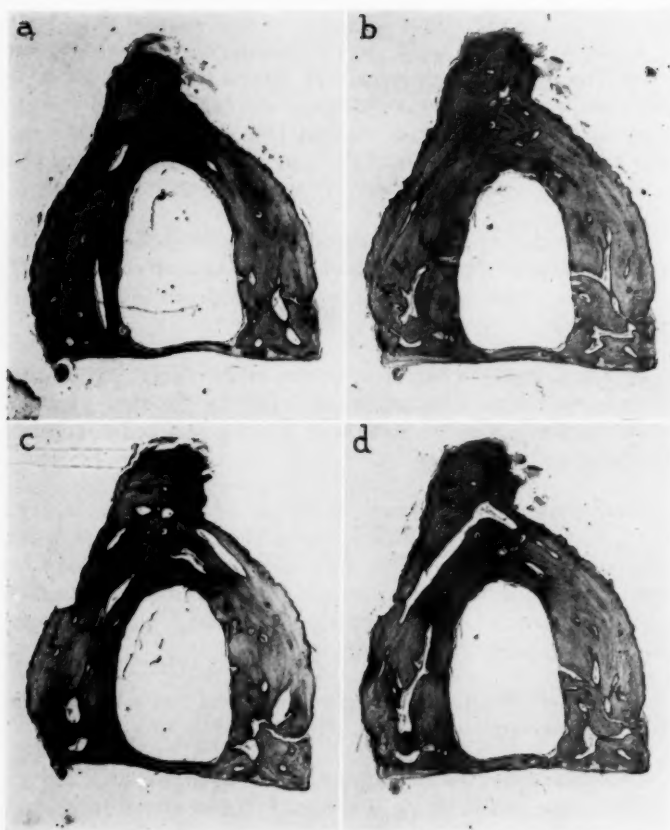


Fig. 8.—Sections of a pathological stapes showing great increase in vascular bone. Specimen kindly provided by Dr. Eugene L. Derlacki, Department of Otolaryngology, Northwestern University Medical School.

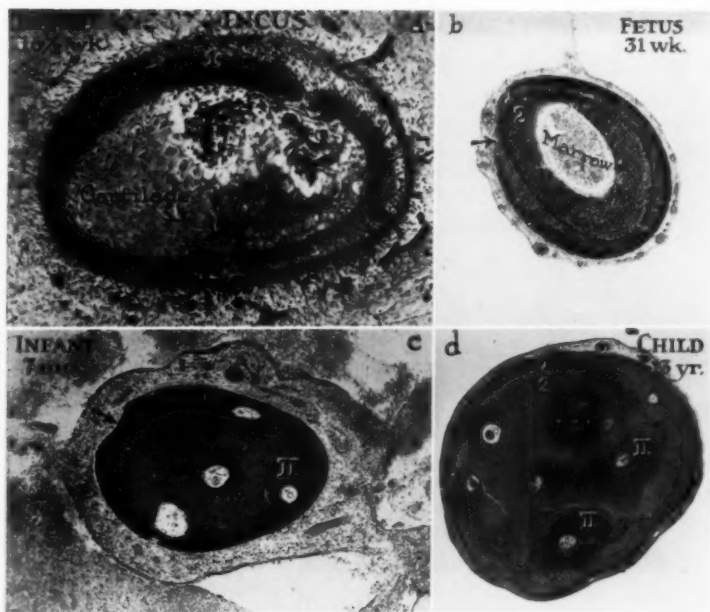


Fig. 9.—Transverse sections selected to record the chief stages in development of the incus. *a*, fetus, 16½ weeks (126 mm); *b*, fetus, 31 weeks (280 mm); *c*, infant, 7 months. X 43. Arabic numbers indicate layers of bone: 1, outer, periosteal; 2, inner, endosteal. In *b* and *c* arrows point to zones of peripheral resorption. In *c* and *d* the Roman numeral II marks areas of secondary formation of bone.

in every specimen of stapes, the other with the retention of a fetal pattern in its osseous part.

Cartilage of the primordial "ossicle" is never normally replaced on either the articular surface of the head or on the vestibular (inner, or labyrinthic) aspect of the base and fenestral (peripheral) margin of the latter (Fig. 6*f*). Comparably, the bone of the stapes, formed during early fetal life, never gives way to haversian bone (thus differing from the pattern of ossification common to the human skeleton generally).

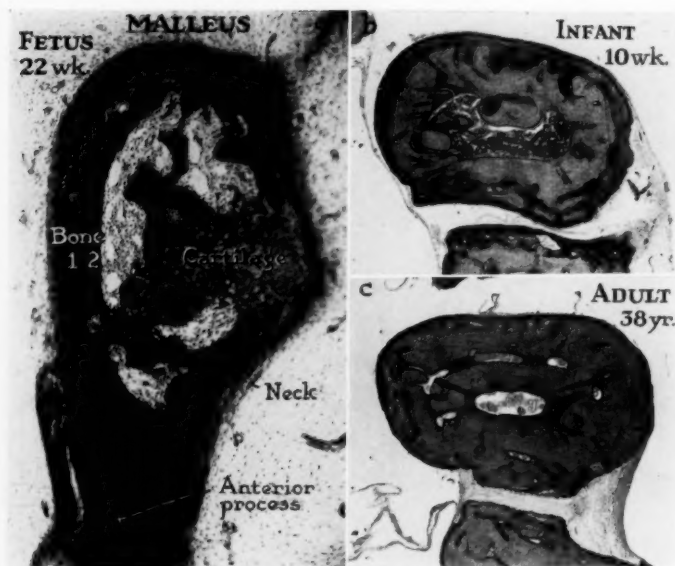


Fig. 10.—Transverse sections selected from otological series to demonstrate three of the major steps in development of the malleus. In *a* the Arabic numerals 1 and 2 are placed, respectively, on the periosteal and endosteal layers. *a*, X 45; *b* and *c*, X 20.

The observations just reviewed account for the thinness of the footplate which, in many instances, consists solely of cartilage in local areas, and for the improbability of adequate healing in a stapes that has been fractured in the course of an operation in endaural surgery.

This means that the stapes never attains the histological architecture which is regularly regarded as mature for a tibia, femur or humerus (to select typical examples); instead of undergoing growth in a long span of twenty or more years between late fetal life and early adulthood, the stapes not only does not grow but, while retaining embryonic and fetal constituents, the ossicle actually sacrifices more than half of its primordial bulk. These circumstances are not to be written off as belonging in the category of esoteric anatomy. On the

contrary, they represent practical hazards in surgery which involves the auditory ossicles.

Equally important is the unpredictable occurrence of aberrancies in form and failure in development of an entire ossicle or of any of its constituent parts (Fig. 7). Such anomalies are the result of deficiency in the blastema derived from the branchial skeleton. Post-natal changes, due to pathology are often profoundly deforming (Fig. 8).

INCUS.—Although the malleus and incus are also of branchial origin, they, unlike the stapes, pass through a strikingly different series of developmental stages on the way to maturity.

Consequently, embryonic, fetal and postnatal changes produce a form and fabric which are the bases of surgical problems unlike those presented by the stapes (Fig. 9). Whereas the risk in manipulation of the stapes is the result of its fragility, the hazard in use of the incus for artificial anchorage of strut or other replacement is one that depends upon long-term "remodelling" and upon the special nature of its blood-supply. These features are established in the course of fetal development of the ossicle.

Bone formation in the incus begins in the 16-week fetus, in advance of the initiation of ossification in the stapes. At a slightly older stage (16½ weeks), the process is actively under way in a manner characteristic of osteogenesis in a typical long bone (Fig. 9a).

In the 19-week fetus, a complete shell of periosteal bone surrounds the long crus of the incus; endochondral bone is forming within a marrow cavity. At approximately the midpoint in intra-uterine life (21 weeks), endochondral bone begins to encroach upon marrow. Unlike the steps followed in morphogenesis of the stapes, the marrow cavity is destined to be obliterated through occupancy by bone, not as a result of replacement by mucosal tissue.

Before birth, the aforementioned process has progressed (in the fetal specimen of 31 weeks) to a point at which the long crus is an almost solid osseous structure (Fig. 9b).

No sooner has the incus matured in respect to form and size than a process of remodelling begins—as demonstrated in specimens of ossicles from the ears of infants (Fig. 9c).

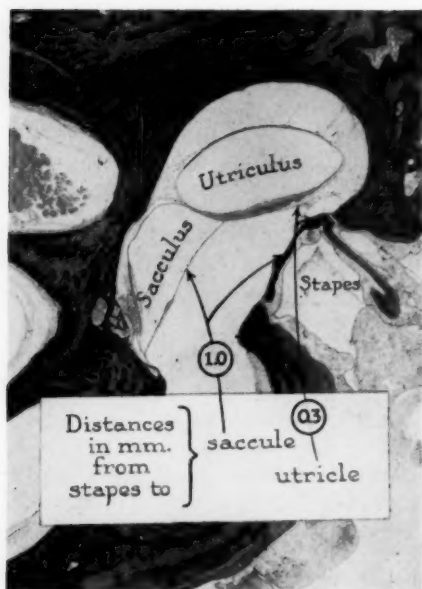


Fig. 11.—Transverse section through the temporal bone of a 6-month infant, with distances measured from the vestibular surface of the footplate to the utricle and the sacculus.

Destruction, followed by reconstruction, continues throughout life, as is evidenced in specimens from children (Fig. 9*d*) and in adults of 60 to 70 years.

All of this means that the changes in the architecture of the incus are life-long; in the stapes, on the contrary, major steps in change of form and fabric have been completed in the fetus. Following precocious and precipitate rush toward maturity, the stapes remains unchanged throughout the individual's lifetime.

Throughout adulthood, blood vessels are present in layers of bone near the surface-layer of the incus (Fig. 9*d*). It therefore seems probable that normal vascularization would be impaired by a

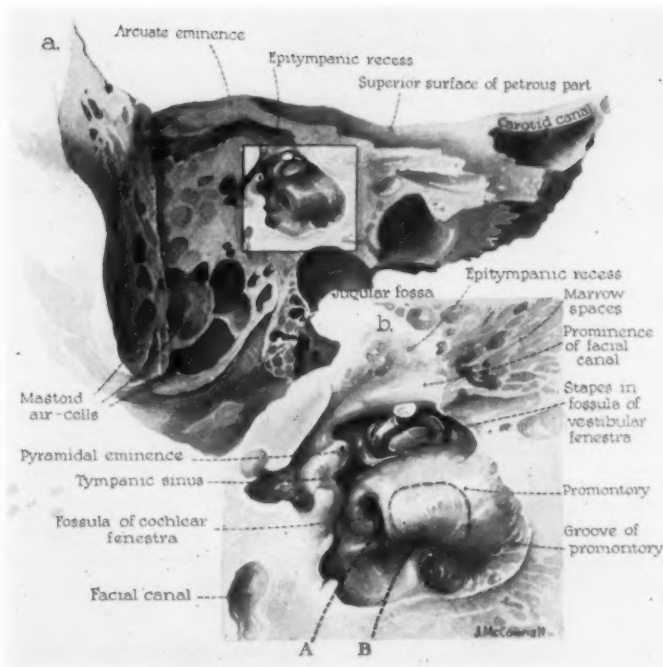


Fig. 12.—Specimen of temporal bone cut through its long axis in order to demonstrate the relations of the cochlear (round) window. The area within the blocked rectangle in *a* is shown in greater detail in *b*. In the later figure *A* indicates the orifice of the *fossula fenestrae cochleae*; *B* points to the portion of the fossular wall (outlined) which is removed in Figure 13*b* to expose the window itself. *a*, X $1\frac{1}{2}$ actual size; *b*, X $4\frac{1}{2}$.

constricting loop applied in surgery, with resultant peripheral necrosis. This means loss of superficial laminae of bone would cause loosening, detachment and reoperation.

MALLEUS.—Like the incus, the malleus seemingly undergoes a life-long succession of changes. The process of bone-formation in the two ossicles is essentially similar.

The malleus ossifies from a single center which is located near the junction of the head with Meckel's cartilage. The center is first noted in the fetus of 16 weeks, in the form of a plaque of periosteal bone. Spreading rapidly (matching progress in the incus), the bone forms a shell in advance of the transformation of the central cartilaginous model (except at the articular surface, at points of ligamentous attachment and over the manubrium).

As soon as the first perichondral bone has been deposited, calcification of the matrix and enlargement of the cells of underlying cartilage take place (Fig. 10*a*). This changed cartilage is then invaded, and completely replaced, by osteogenic tissue. Toward the end of intrauterine life, endochondral bone is deposited on the surface of intrachondrial islands and along the inner margin of the perichondral shell.

With the exception of the manubrium and the anterior process, the malleus resembles the incus but differs from the stapes (Figs. 10*b* and 10*c*).³ Like the incus, the malleus possesses a series of circumferentially arranged vascular channels, around the remnant of a central marrow cavity; further resembling the incus, the malleus is remodelled during adulthood, showing areas of bone-erosion and subsequent formation of secondary and tertiary bone (Fig. 10*c*).⁴

³ Osteogenic tissue invades the center of the manubrium, spreading from the head of the ossicle. In this way, the center of the manubrium becomes endochondral bone, leaving permanently a peripheral rim of the original cartilage.

Remarkably precocious in development, the anterior process is formed in bone when the ossicles have just acquired definitive form in cartilage, in the 8-week stage. The rod of bone is then almost as large as it is in the fetus of 120 mm, at which stage perichondral bone is just beginning to form in the adjacent portion of the head of the malleus. Thereafter it increases in length, keeping pace, as it were, with the growth of the three ossicles. The anterior process finally fuses with the malleus proper in the fetus of 22 weeks—appearing as a lancet along the caudal aspect of the bulkier first branchial bar (Meckel's cartilage).

⁴ Figure 10*c* demonstrates strikingly the annular arrangement of vascular channels in the malleus; figure 9*d*, selected to emphasize the feature of rebuilding, does not satisfactorily record the frequency with which the canals for the blood-vessels occupy the zone between the two layers of bone. This characteristic is illustrated in figures 6 to 9 in the Quarterly Bulletin of Northwestern University Medical School, vol. 33, pp. 110-119, 1959. Figures 10*a* to 10*c* are taken from a set of photomicrographs in a comparable article on the malleus which will appear in the same journal. Articles of the stapes and the otic capsule have already been published (vol. 33, pp. 44-59, 1959; vol. 32, pp. 157-172, 1958).

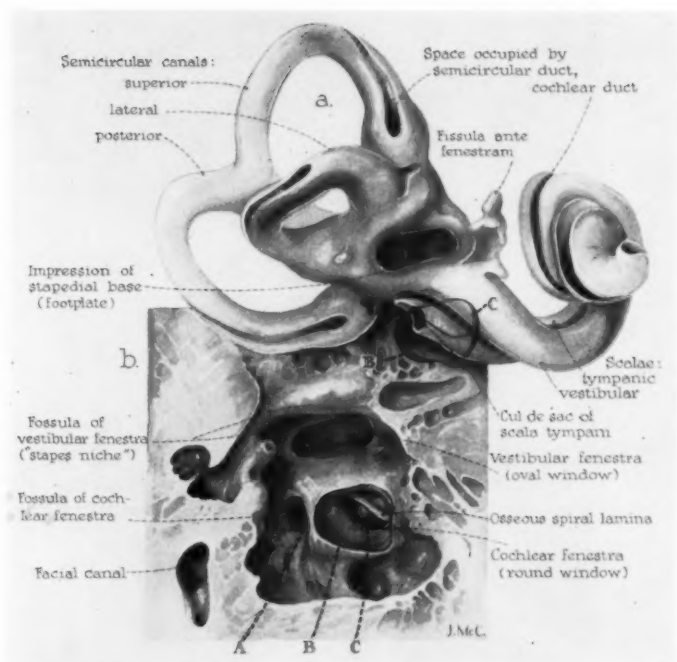


Fig. 13.—Reconstruction of the perilymphatic labyrinth and specimen of temporal bone (as in Figure 12), showing form of the round window and its relation to the space of the fossula and to the scala tympani. The lettered leaders point to structures as follows: A, to the aditus to the fossula; B, to the margin of the artificial opening in the tympanic wall of the fossula (compare Figure 12*b*); C, to the margin of the round window (superimposed upon the reconstruction in Figure 13*a*). *a*, X 6; *b*, X 4½.

d. *Membranous Labyrinth* (Fig. 1, at E). As discussed at last year's meeting of the Society, the distances between the stapedial footplate (Fig. 1, at E) and the various parts of the membranous (endolymphatic) labyrinth are excessively small; as a consequence, probes inserted through the stapes may readily penetrate vital parts. For example, a distance of 2 mm intervenes between the stapedial footplate and the utricle, an even shorter distance separates the footplate from the stapes from the saccule (Fig. 3, inset). At the transverse level

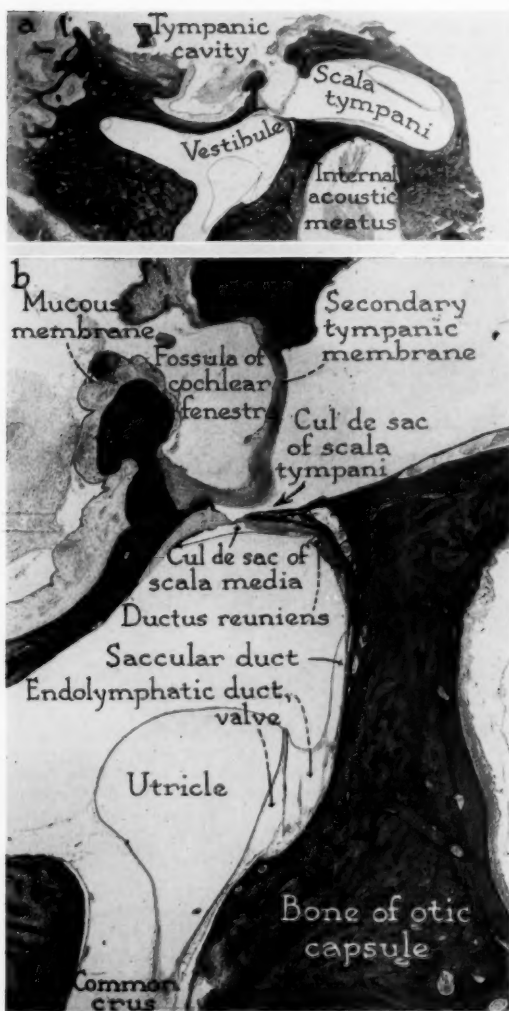


Fig. 14.—Transverse section through the petrous part of the temporal bone from a newborn infant. *a*, the inclusive field, for guidance in orientation. *b*, details of anatomical structure and interrelationship of spaces and membranes in the general region of the fossula of the cochlear fenestra. *a*, X 12; *b*, X 16.

of the posterior crus of the stapes the intervening distance may be disturbingly small (Fig. 11).

c. *Fenestra* (Fig. 1, at E). Changes in the stapes accompany otosclerotic involvement of the bone which surrounds the oval window (Fig. 1, at F).

New interest in the histological structure of the fenestral wall has been aroused by statistical records on localization of sclerotic bone provided by Dr. Eugene Derlacki from the Department of Otolaryngology of Chicago Wesley Memorial Hospital and by re-examination of serial sections in the J. Gordon Wilson Collection at Northwestern University Medical School.

Pre-operative examination of the stapedia region in 400 consecutive cases served to strengthen the notion that the ante-fenestral area is the predilective site for otosclerotic change. In the 200 consecutive cases of otosclerosis the anterior portion of the fenestra (adjacent to the stapes) was invariably involved. In 48 per cent of the cases the pathology was limited to that area; the superior margin was also effected in 4 per cent, the inferior margin in 7 per cent, both margins in 4 per cent, the anterior as well as the posterior border in 10 per cent. The lesion was circumferential in 4 per cent; in 23 per cent of cases the otosclerotic involvement was total, surrounding the fenestra and covering the entire footplate of the stapes.

The study of 50 serially sectioned temporal bones from late fetuses, infants and children (to the age of 10 years) revealed a remarkably high occurrence of a cartilage mass (chondroma) in the normal location of the fissular channel.⁵

It seems likely that these circumstances (both of them representing aberrancy) are causally linked, rather than being conditions due to chance.

II. STRUCTURES NEAR COCHLEAR (ROUND) FENESTRA

a. *Fenestra* (Fig. 1, at G). The cochlear fenestra (round window) is situated on the inner wall of a concavity, the *fossula fenestrae*

⁵ Several articles on the subject of normal and pathological structure of the otic capsule in the region of the fissula ante fenestram have appeared in earlier issues of this journal (vol. 56, pp. 957-985, 1947; vol. 57, pp. 103-128, 1948).

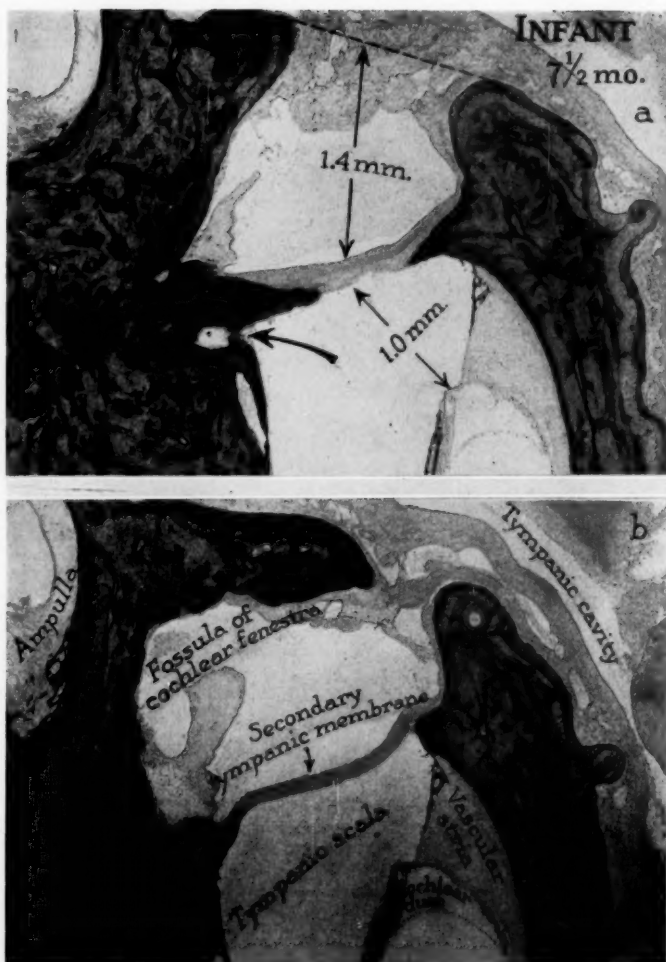


Fig. 15.—Transverse sections through the temporal bone from a young infant. In *a*, the surgically important interdistances are recorded; in *b*, the spaces (tympanic and labyrinthine) and the membranes are labelled. *a*, *b*, X 24.

cochleae (Fig. 1, at G). In the fresh state it is closed by the secondary tympanic membrane (Figs. 14 and 15). In the dried bone, freed of soft tissues, the space of the fossula is continuous with that of the basal coil of the cochlea (Figs. 12 and 13).

The fossula of the round window differs from that of the oval (vestibular) window in respect to the following features: it is closed by nothing more substantial than a membrane (whereas the oval window is occupied by an ossicle which is held strongly in place by the annular ligament); it is protected by the tympanic wall of bone (whereas the stapes rests in a niche bounded by the canal for the facial nerve, the semicanal for the tensor tympani muscle and the promontory of the cochlea). In a comparable way, the two orifices differ surgically: the oval window is the direct objective in all operations on the stapes and in the procedure designed to provide an artificial fenestra in the wall of the perilymphatic labyrinth; the round window, purposefully avoided, would be affected only in instances of incautious packing, forceful aspiration or unguarded instrumentation—perilymphatic space thus being entered through rupture of the secondary tympanic membrane (Figs. 14*b* and 15*b*).

b. Labyrinths and Membranes. No matter whether an instrument (upon rupturing the membrane) happened to be turned in the direction of the basal coil of the cochlea (Fig. 15*b*) or in that of the vestibule (Fig. 14*b*), loss of perilymphatic fluid from the tympanic scala would be the result.

Were the instrument pushed into the basal cochlear turn for a distance of 1.0 mm beyond the fenestra (and membrane), it could perforate the cochlear duct (Fig. 15*a*), with consequent loss of perilymph.

Should such an instrument be directed toward the vestibule (which is continuous with the scala vestibuli), the following spaces and membranes would be encountered (Fig. 14*b*): the cul-de-sac of the scala tympani; the basilar membrane (stretched across the hiatus between the primary and secondary spiral laminae); the cul-de-sac of the cochlear duct (continuous with the ductus reuniens, saccular duct and utricle); the vestibular portion of the perilymphatic space.

As mentioned above, even though the round window is not a site of surgery, vital parts of the membranous labyrinth might be

injured as a result either of careless packing of the middle ear, or of inadvertent instrumentation; similarly they could be ruptured in forceful aspiration.

c. *Perilymphatic Duct*. Developmentally, the so-called perilymphatic (periotic) "duct" is an appendage of the perilymphatic labyrinth. Being nonepithelial, it is not a true duct; rather, it is a series of communicating spaces within an arachnoidal type of connective tissue, and its tissue is continuous with that of the tympanic scala. Grossly, the tissue occupies the cochlear aqueduct (*canaliculus cochleae*), which originates near the beginning of the bony cochlear canal (Fig. 15a, at unlabelled arrow), and terminates on the inferior surface of the petrous pyramid between the jugular fossa and the opening of the carotid canal.

Being part of the perilymphatic system, the histogenesis is similar to that of the tympanic and vestibular scalae.

The perilymphatic channel makes its first appearance in the fetus of 11 weeks as an area of rarefaction in mesenchymal tissue, continuously internally with the periotic tissue of the scala tympani and externally with that of the primordial meninges.

In the 17-week fetus, ossification centers appear in the wall of the future canaliculus.

In specimens four weeks older (21 weeks, or approximately mid-term), bone-formation results in the production of a true cochlear canaliculus. Contrary to conventional descriptions, the canal is separate from the channel which transmits the cochlear vein.

Surgical interference in this area of neural, vascular and perilymphatic anatomy not only involves technical hazard, but also may interfere with normal cerebrospinal physiology of the fluid-system. The fractional part played by the duct in maintenance of fluid-balance is now a matter of speculation; there are other lymphovascular communications whose service may render that of the perilymphatic duct merely contributory.

SUMMARY

An attempt has been made to bring together descriptions of those features of otological anatomy which, in recent studies by the

author and his colleagues, have been found to contribute to the hazards of endaural surgery in cases of otosclerosis.

It has been pointed out that, in an attempt to enlarge the fossula (or niche) in which the stapes is lodged, the facial nerve and the cochlea are endangered; and that, because of its fragile architecture and relation to the parts of the membranous labyrinth contained in the vestibule, removal of the stapes must be carried out with extreme care. Additionally, observations on the vascularization of the ossicles have been recorded—in reference to techniques in prosthesis.

Although it is recognized that the structures within and near the fossula of the round window may be unintentionally involved in middle-ear surgery, similarities and differences between the two fossulae are discussed.

In every instance the approach is made on developmental basis, because no matter whether the immediate problem confronting the surgeon is owing to the differing architecture of the stapes and incus, to the submucosal (exposed) position of the facial nerve, or to the peculiar lamination of the cochlear capsule, the circumstance is dependent upon formative steps taken during fetal life. In many important respects, the ossicles as well as parts of petrous and tympanic divisions of the temporal bone, retain their prenatal form and fabric.

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JAMES HOYT MAXWELL

1901 - 1960

James Hoyt Maxwell was born in Paw Paw, Michigan, on December 15, 1901, the son of John Charles Maxwell and Cleo Lyle Stevens Maxwell. His father was a hard working practitioner of medicine who believed in honest toil and dedicated his long and arduous life of 85 years to study, civic interests and humanitarian service. Dr. Maxwell's boyhood home was a place of culture and refinement where the influence of medicine was constantly a motivating inspiration.

He attended high school in Paw Paw and then the University of Medicine where he received an A.B. degree in 1924. He graduated from the University of Michigan Medical School in 1927 with a notable record which earned memberships for him in Alpha Omega Alpha, Phi Beta Kappa and Phi Kappa Phi.

From the beginning of his medical studies he wanted a chance to train in the field of Otolaryngology and to have a career in academic medicine. His industry, motivation and fine spirit of cooperation impressed his professors and led promptly to his appointment to a rotation internship in the University of Michigan from 1927 to 1928 and residencies in Otolaryngology from 1928 to 1932. He began his academic career in Medicine in the University of Michigan Medical School as an Assistant Professor of Otolaryngology in 1933; seven years later he was given the rank of Associate Professor. In 1945 he was elevated to the rank of Professor of Otolaryngology and on July 1, 1958, he was appointed Chairman of the Department, a position he held until his death on June 2, 1960.

Thus we note that Dr. Maxwell played a major role in the growth and development of the Medical Center and the Department of Otolaryngology at the University of Michigan for more than thirty years. During this period he never missed an opportunity for service. He possessed innate optimism and a constant eagerness to study and learn which reflected itself on all occasions in his teaching and clinical activities. He would settle for nothing less than perfect accomplishments.

Dr. Maxwell joined the editorial staff of the ANNALS in 1957 and proved a valuable consultant in the phases of otolaryngology which



JAMES HOYT MAXWELL

were of special interest to him. Through the years he contributed many notable articles, latterly upon the salivary apparatus, on which he was an authority.

On February 15, 1936, Dr. Maxwell married Marjorie Arnold. His marriage played an important role in his growth and progress in academic life. The two of them joined in mutual understanding and tolerance, aiding and encouraging each other in making their home a place of refinement for their two sons, Robert and John. Dr. Maxwell's work was always something to be respected and encouraged by the indulgent members of his family.

Dr. Maxwell provided a large measure of leadership in programs of undergraduate and graduate medical education. He was ready at all times to make the latest information available to his students and members of his staff. He had the ability to make his residents strong by precept and example and by pointing the way to a realistic and practical application. He demanded that his staff be ready to challenge authority, acquire resourcefulness and pursue independent thinking. His kindly manner, uncommon diagnostic skill and rare solicitousness for the welfare of his patients commanded the respect and admiration of his friends and colleagues everywhere.

A.C.F.

Abstracts of Current Articles

EAR

Clinical Studies on DL Difference Test

Tsugawa, K.: J. of Oto-rhino-laryng. Soc. of Japan 63:99 (Jan.) 1960.

The author examined the clinical usefulness of the DLD test in establishing the presence of the recruitment phenomenon.

The following results were obtained in a study of 50 normal ears and 209 ears with various types of impaired hearing with Maico MA-1 hearing evaluator.

1. DL at 10 db over the threshold showed slight individual difference, but DL at 40 db over the threshold and DLD hardly showed any individual difference.

2. The minimal limits of DLD in the normal ears were 0.6 db in 250 cps; 0.6 db 500 cps; 0.6 db 1000 cps; 0.5 db 2000 cps; 0.5 db 4000 cps.

3. The standard deviation of DLD by the frequency was small compared with DL, showing the least value at 1000 cps. For this reason 1000 cps was the preferable test frequency.

4. In the conductive deafness group, 73 ears (96%) out of 76 proved to be recruitment negative; in combined deafness, 64% were negative. In the perceptive deafness group, 66 (66%) out of 100 ears proved to be recruitment positive while the other 34 were negative.

The DLD test was found reliable, and the authors believe that this method has much clinical value in the differential diagnosis of perceptive hearing impairment.

HARA AND OGURA

Evoked Potential of Non-Anesthetized Rabbit Brain to Acoustic Stimulus and Its Application to Measurement of Hearing

Suzuki, Y.: *J. of Oto-rhino-laryng. Soc. of Japan* 63:24 (Jan.) 1960.

The author investigated the evoked potential which was found in the non-anesthetized rabbit brain by sound stimuli. The study was to measure the threshold of hearing on experimental animals. The observation was carried out by automatic superimposing technique using a photo-transister.

The curve of the minimum reaction value to the acoustic stimuli which ranged from 250 to 8000 cps, with an interval of 10 sec and an 0.5 sec stimulating time was shown by audiogram. The average value of each cycle obtained was between 50 and 60 db.

Having used a 1000 cps tone to mask the 3000 cps testing tone, the reaction threshold of the masked tone rose to 80 db generally, and a difference of 10 to 20 db was seen in comparison with the human ear.

The author concluded that the above evoked potential would be an index of the measurement of hearing in the rabbit.

HARA AND OGURA

Studies on the Second Phase of Nystagmus

Noto, A.: *J. of Oto-rhino-laryng. Soc. of Japan* 63:40 (Jan.) 1960.

The secondary phase is one of the fundamental patterns of nystagmus, but usually hidden in the presence of such inhibitory factors as vision or noise. It was thought to be constituted by the primitive tracts in the brain stem which are constantly influenced by the higher regulating vestibular nystagmus tracts in the cerebrum and cerebellum.

The minimal stimuli necessary to induce secondary nystagmus seemed to vary even in the same subject under different conditions.

The author studied this phenomenon with the use of an electrically driven rotatory chair and electro-nystagmograph on human as well as experimental animals.

The second phase of nystagmus in humans appeared in 100% with rotatory, in 72% with caloric and in 80% with optokinetic stimuli. In rabbits it appeared in 30% with rotatory, in 78% with caloric and in 100% with optokinetic stimuli.

HARA AND OGURA

Biochemistry of Perilymph in Otosclerosis

Wullstein, H. L., Kley, W., Rauch, S., and Koestlin, A.: *Z. Laryng. Rhinol.* 39: 667-672, 1960.

This is a preliminary report. Samples of perilymph were obtained during the course of stapedectomies in otosclerotic patients with the aid of small capillary tubes (glass or plastic). The amount varied between 8 and 20 microliters. In 22 cases, sodium potassium and alkaline phosphatase were determined. The sodium and potassium levels were found within normal ranges, although potassium levels were indeterminable whenever there was more than 2% blood in the sample, which, of course, was unavoidable in some cases. Alkaline phosphatase, not normally present in perilymph, was found in all ten cases in which its determination was possible. As a rule its level was found higher in the perilymph than in the peripheral blood (where higher-than-normal values are known to exist in certain bone and other diseases). Therefore, the appearance of alkaline phosphatase in the perilymph cannot be explained on the basis of a systemic change. The authors are of the opinion that the alkaline phosphatase level in the perilymph may possibly reflect the state of activity of the otosclerotic process (being the sign of a localized osseous disease process) and will report on this point at a later date. The studies will also be extended to include other factors, the blood levels of which are known to alter with diseases of the bone.

TONNDORF

The Initial Stages of Histological Otosclerosis

Weber, M.: *Z. Laryng.* 39:521-533, 1960.

M. Weber is by no means a newcomer to the field of otosclerosis. In the early thirties, he had made a name for himself by drawing attention to the histological similarities between otosclerosis and osteitis fibrosa (cf., for example, this journal 42:433-453, 1933, "The Blue Mantles in Otosclerosis: A Contribution to the Pathology of the

Labyrinthine Capsule"). The present article is written with the authority of about 30 years' experience in the study of histological otosclerosis.

In the first portion, the author summarizes the structural properties of manifest (histological) otosclerosis: The maturing of the actual focus from its early (growing) to its terminal (arrested) state. Since the perivascular blue mantles show a very similar maturing process, according to the author, he is of the opinion that the events going on in the foci and in the blue mantles are basically identical.

In agreement with others, the author found that otosclerotic foci as a rule develop from islands of persistent cartilage within the otic capsule, that is, from living cartilage cells which are in the process of dying, not from calcified ground substance (globuli ossei). The surrounding bone is absorbed with the aid of giant cells while the new otosclerotic bone is put down in the lacunae of Howship.

The author stresses the point that the blue mantles (the name was first proposed by Manasse in 1912) are not identical to what he calls "blue sleeves" (*blaue Saeume*). Such a sleeve is a normal isolating layer of bone surrounding any vascular spaces. These sleeves may vanish, for no apparent reason, to be substituted by loose connective tissue. This resorption is again due to the action of giant cells and the defect is finally filled in by newly formed otosclerotic bone.

The author closes his article by posing the following questions: 1) Why are there islands of living cartilage in the otic capsule? (To this I think competent zoologists have an answer: they may be remnants of fissures between the various bones contributing to the formation of the otic capsule.—Rev.) 2) Why do these cartilage remnants die in some cases? 3) Why do giant cells appear in the resorption processes which are triggered by Question 2)? 4) Why is, then, within the defects formed by the event under Question 3), a new bone put down which is different in its make-up as to cells, fibrils, and ground substance?

TONNDORF

New Aspects of the Biology and Pathology of the Inner Ear

Vosteen, K. H.: Archiv Ohren- usw. Heilk. u. Z. Hals- usw. Heilk. 178:1-104, 1961; 50 figs.

A word of explanation may first be in order as to the nature of the paper under discussion. Instead of the customary "symposium"

of American meetings, German Medical Societies request one or two of their members (or guests) each year to present a "Referat" (a review), each on a selected topic. These papers are then given at the next year's meeting. Each is followed by additional invited and contributed papers. The "Referat" itself appears in print several weeks ahead of the meeting so that contributors and would-be discussors can peruse it before hand. Dr. Vosteen's present paper was this year's "Referat." The meeting was held in Freiburg i. Br., May 14-18, 1961.

The reviewer had the pleasure of both listening to the verbal delivery and reading the printed version. Dr. Vosteen was picked for the present topic in recognition of his own work on intracochlear enzymes (cf. for example *Laryngoscope* 70:351, 1960), and an excellent choice it turned out to be.

The accent of this paper is of course on cochlear biochemistry and metabolism at rest and under various stresses (acoustic stimulation and overstimulation, hypoxia, hypoxydosis, etc.). However, author takes up his thread with a discussion of the electrical cochlear phenomena. This is followed by the endocochlear electrolytes. Next is the metabolism with reference to the production of energy. (Evidence is given here for the first time of certain enzymes (e.g. Lactathydrogenase) which indicates that, in addition to their normal aerobic metabolism, the haircells may fall back upon anaerobic processes when the need arises. The latter processes are not unlike those taking place in muscular tissue.) The final chapter treats the role of acetylcholin. Each point is discussed from the (often divergent) standpoint of numerous investigators. (The list of references contains 275 papers.) If one wants to quibble, in some sections too much space is given perhaps to citing mere speculating articles to which experimental support is lacking. However, there is never any doubt about the nature of such papers.

With its lucid style, its broad and rational approach, and its critical appraisal this lengthy article is highly recommended.

At the meeting, in addition to Vosteen's presentation two invited papers (S. Rauch and H. Engstroem) were given and followed by eight contributed papers. From this number and from the subsequent discussion one gained the distinct impression that the interest in biochemical aspects of inner-ear function is very active in Germany today.

TONNDORF

- 1) Das Gehoerorgan der Wirbeltiere und des Menschen, Beispiel fuer eine vergleichende Morphologie der Lagebeziehungen (The Hearing Organ in Vertebrate Animals and in Man; an Example of a Comparative Morphology of Topographical Correlations)

Werner, Cl. F.: Geo. Thieme, 310 pp., 150 figs., 1960.

- 2) The Structure and Function of the Middle Ear

Kirikae, Ichiro: University of Tokyo Press, 157 pp., 111 figs., 1960.

The title of the book by Werner is an obvious extension of Retzius' classic: "The Hearing Organ of Vertebrate Animals." Being 80 years younger the new book as one might expect goes much beyond the confines of the older one. But since Retzius' book with its excellent and accurate drawings can hardly be superseded, the new book supplements the older one and treats the entire subject from a different angle. The ear is described, part for part, in its variations through different species. In doing so, much stress is laid upon correlations, i.e. the mutual influence of neighboring structures upon each other.

Such a study in phylogeny demonstrates the variety of experimentation Nature has undertaken in the course of evolution of one organ. Apparently, not all of these steps were "successful," for some of them (e.g. the Weberian ossicles of the *ostariophysi*) ended in dead-end streets. This points to the fact that human embryology (or that of any other species for that matter) is not a repetition of the entire phylogeny but merely develops along one of its many and variegated branches.

Dr. Werner is a comparative zoologist and his interest in the ear is of long standing. In 1940, he published another book, "The Labyrinth," which treated in a systematic manner the special histological methods peculiar to the preparation of the temporal bone and its contained structures (much of this based upon Werner's own painstaking efforts) as well as the effects of various noxious agents upon these structures. The new book joins a distinguished company and is highly recommended as a reference book to all students of the ear.

The book by Kirikae is in a different vein. It presents the author's view on the morphology and physiology of the middle ear, that part of the organ upon which the attention of otologists is presently focused. Thus this is a very timely book and since much of its content is based upon, or at least supplemented by, the author's own studies, it speaks with considerable authority. Part of this book (on Bone Conduction) has appeared in English before in a supplement of *Acta Otolaryng.*, No. 145, 1959.

The poor translation of the book is much to be regretted. At best, reading it is cumbersome; at worst, things are left open to the reader's own interpretation.

These two books were grouped together here for the following reason: Werner, in a brief remark, is highly critical of attempts to explain function on the basis of model experimentation. In his opinion such simplified models often neglect fine structural details. Kirikae, on the other hand, has made much use of model experiments, a point which has been met with raised eyebrows by at least one other reviewer (Archive of Otolaryng., Feb. 1961). To this the present reviewer wishes to make some remarks. Model experimentation is a time-tested tool of investigation in such engineering fields as ship and airplane construction. There, any experimentation on the real structure is either too costly or virtually impossible. From these two fields rules have been developed which come under the general heading of Dimensional Analysis. They require physical similarity between a given system and its model which is often gained at the expense of structural similarity. Such models permit studies of the effects caused by systematic variation of different parameters thereby deriving rules of general validity. (In experimental animals, such studies are not always feasible since structural parameters can be varied only in a limited manner.) When a morphologist concludes that a given structure may have such and such a function, he has in fact constructed a conceptual model. By analogy, he has assumed that his structure acts similar to others familiar to him. However, analogies based upon model studies permit much more sophisticated conclusions, and more often than not, yield results which are totally unexpected. This is especially so with regard to *dynamic* functions.

The point to be made is that neither method can provide all the answers. Biology after all is a synthesis of morphology and physiology and physiology frequently has to attack its problems in an indirect manner such as by making model studies.

TONNDORF

Observations on Sympathectomy in the Treatment of Ménière's Disease

Golding-Wood, P. H.: J. Laryng. and Otol. 74:951-971 (Dec.) 1960.

The author reviews the objections to sympathectomy and discusses the types performed. He makes use of an anterior approach resecting the stellate ganglion and upper two thoracic ganglia bilat-

erally. He has performed the operation in 430 cases of which 148 had Ménière's, with no deaths and little morbidity. He presents results in 93 cases of Ménière's followed 2½ to 7 years, all of which were medical failures. The vertigo ceased or improved in 79, the hearing improved in 68, and the tinnitus improved in 63. He states that the bilateral Horner's syndrome usually passes unnoticed; there was some nasal congestion, and pain in the arm and shoulder which always clears eventually. He feels the best cases are those of middle age, with severe vertigo, unaccompanied by hearing loss of more than moderate degree. The procedure should be done early to preserve hearing.

He feels the best prognostic signs are a definite but inadequate response to nicotinic acid, and the relief of "head symptoms" by stellate ganglion block. The "head symptoms" were vague, but usually a unilateral occipital or temporal headache or "cotton" feeling.

In 51 patients with a satisfactory xylocaine stellate block (Horner's syndrome produced), 14 were relieved of tinnitus, the pure tone audiogram was slightly elevated in 11, and 21 of the 32 complaining of "head symptoms" improved. He abandoned this as a preliminary test from 1952-1956, but thinks the "head symptom" improvement of prognostic significance.

He states that sympathectomy is not competitive with labyrinthectomy, which is preferable for unilateral disease. Eight case reports are presented in detail.

TRIBLE

Xanthoma of the Mastoid (Xantoma de la Mastoides)

Poch-Viñals, R.: Acta O.R.L. Ibero-Americana 11:5:417-447, 1960.

The author presents a case of mastoid xanthoma in which two surgical interventions were performed through a postauricular approach. There was extensive destruction of the mastoid and dural exposure. Whereas cholesterol values were normal during the immediate postoperative period, a hypercholesteremia (up to 450 mg%) eventually developed.

The author speculates on the significance of this development, questioning the possibility of cholesterol accumulating in a focus, and later appearing in abnormal amounts in the blood stream when

the focus was removed. He suggests doing cholesterol studies on any future cases.

Points of differential diagnosis are discussed, pertinent to such conditions as eosinophilic granuloma, Hand-Schüller-Christian disease and cholesteatoma.

ALFARO

Aural Cholesteatoma (Sobre el Colesteatoma de oído)

Cavaller, F.: Acta O.R.L. Ibero-Americana 11:5:464-69, 1960.

The author stresses two important aspects of cholesteatoma: 1) intracranial complications of great severity are frequent in chronic cholesteatoma of the ear; 2) a history of chronic suppuration is frequently absent. Seven case reports are presented. Three points in surgical techniques are mentioned: the author prefers the postauricular approach; he does not use skin grafts to line the cavity; and he advocates extirpation of brain abscesses by a neuro-surgeon in preference to drainage through the mastoid by the otologist.

ALFARO

On the Change of Voice, Speech, Intelligence in a Deaf-Mute Following the Operative Restoration of Hearing

Satomi, S.: J. of Oto-rhino-laryng. Soc. of Japan 63:76 (Jan.) 1960.

The author reported a 13-year-old deaf-mute boy who showed remarkable improvement in his voice, speech and intelligence after obtaining better hearing by a successful fenestration.

He had 65 db hearing loss in the right ear and 75 db in the left side due to bilateral congenital malformation of the external and middle ears. As his bone conduction hearing was normal a fenestration was done on the right side. The hearing test done 3 months after the operation showed recovery of hearing to the 25 db level.

The improvement after surgery was rapid. In not more than a half year the differential sensitivity in pitch and intensity of sound was found to be normal. The pronunciation of individual words became correct, as checked with a sonograph analyzing every syllable

of the words. But the conversation was not improved as much as expected. I.A. according to WISC was 54 two months after surgery but improved up to 72 six months after the operation.

HARA and OGURA

Studies on Hearing Disorders in Telephone Operators

Hagino, S.: J. of Oto-rhino-laryng. Soc. of Japan 63:109 (Jan.) 1960.

In view of the possibility of occupational deafness in telephone operators, the author tested the hearing of 498 telephone operators in northern Japan.

He found hearing disorders in 16% among them. And over 80% of the impaired hearing was of a perceptive nature. Moreover, about 50% of the perceptive deafness cases seemed to have a causal relationship to the use of the telephone-receiver. In more than 90% of them the hearing loss was slight, less than 30 db in average.

The incidence was remarkable in males who had been working over 5 years. The operators who had been working less than 5 years showed less than 10 db hearing loss in average.

The author found that the pattern was most commonly a dip at c4.

By detailed examination 70% of the cases showed positive DL.

In conclusion the author feels that hearing disorders of telephone operators have the characteristics of a perceptive loss around 1000 cps and that they may be caused by too much exposure to this tone from the telephone receiver.

HARA and OGURA

Two Cases of Audiogenic Epilepsy

Shimura, H.: J. of Oto-rhino-laryng. Soc. of Japan 63:87 (Jan.) 1960.

So-called audiogenic epilepsy seems to be a rare disease.

The author reported two cases which followed head injury. Both cases had organic lesions in their right temporo-parietal lobe. Hearing test revealed perceptive deafness in both cases. The same epileptic attacks appeared when sound stimuli were given to their left ears. The

sound stimuli had to be at 4000 cps with 40 db or more of loudness. Electroencephalograph showed typical waves of epilepsy.

The conclusion was that the disturbance in the temporal lobe and auditory organs played an important role in these episodes.

HARA and OGURA

**Removal of the Footplate with Reconstruction of the Conductive Apparatus
(La Platinectomie avec Reconstruction de l'appareil de conduction)**

Guillon, H.: Les Annals d'Oto-Laryngologie 78:17-27 (Jan.-Feb.) 1960.

The author briefly mentions various original techniques used prior to the presented method. He also reviews the different methods of approach used in the stapes surgery in the United States and Europe. Like Michael Portman and J. J. Shea, he prefers stapedectomy and vein grafting; he reserves mobilization of the stapes to the early cases.

The author believes that stapedectomy is not any more dangerous than the other methods. The only danger is losing fragments of the footplate in the vestibule. He reviews the findings of B. J. Anson and T. H. Bast in reference to the close proximity of the utricle, cochlear canal and saccule to the oval window, and he cautions the surgeon. He thinks malformation of the membranous labyrinth is responsible for inundation of the middle ear by perilymphatic fluid during surgery. The only contraindications to the surgery are the age of the patient, hypertension and uncontrollable bleeding tendencies. He prefers not to operate on patients with cochlear function below 45 db. Also, the author accepts complete closure of the oval window niche by thick otosclerosis as a contraindication to the oval window surgery.

GOZUM

NOSE

A Study of the Fibrinolytic Activity in Extracts of Nasal Mucous Membrane and Related Tissues

Sasaki, Y.: J. of Oto-rhino-laryng. Soc. of Japan 63:67 (Jan.) 1960.

The fibrinolytic activities of nasal mucosa and related tissues were measured in isotonic saline extract. The tissues used were mucosal

lining of the maxillary sinus, inferior turbinate, nasal polyp, faucial tonsil, pharyngeal tonsil and mucous membrane of the stomach; these were surgically taken from patients having diseases in these areas; i.e., sinusitis, tonsillitis, gastritis, gastric ulcer and gastric cancer.

The results obtained were as follows:

1. The strongest fibrinolytic activity was found in the inferior turbinate.
2. The mucosa of the maxillary sinus had the strongest activity next to the inferior turbinate.
3. Fibrinolytic activity was weaker in the nasal polyp.
4. No activity in the faucial tonsil, pharyngeal tonsil and the stomach.
5. The fibrinolytic activity in the extract of nasal mucosa using isotonic saline solution was found in the globulin fraction, and not in the albumin fraction.

HARA AND OGURA

Notices

UNIVERSITY OF ILLINOIS

The University of Illinois College of Medicine Department of Otolaryngology will offer an intensive postgraduate basic and clinical program under the direction of Doctor Emanuel M. Skolnok. This Assembly for practicing otolaryngologists offers a compact program of one week of daytime and evening sessions. Review of basic morphologic features under the direction of Doctor Maurice F. Snitman and Doctor Frederic J. Pollock is also included.

Interested physicians should write direct to the Department of Otolaryngology, University of Illinois College of Medicine, 1853 West Polk Street, Chicago 12, Illinois.

SIXTH INTERNATIONAL CONGRESS OF AUDIOLOGY

The sixth International Congress of Audiology will be held in Leyden, The Netherlands, from September 5 to 8, 1962. The president is Prof. Dr. H.A.E. van Dishoeck, and the secretary Dr. A. Spoor.

Three round-table talks are planned, with associated and free papers. The subject of the round tables are: "Frequency Analysis of the Normal and Pathological Ear." Moderator: Prof. Dr. G. von Békésy; "Central Deafness in Children," Moderator: Prof. Dr. J. M. Tato; "Psychogenic Deafness and Simulation," Moderator: Prof. Dr. H.A.E. van Dishoeck.

Official languages of the Congress are English, French, German and Spanish. Working languages will be English and French.

The address of the secretariat is: Ear-Nose-Throat Department, Academisch Ziekenhuis, Leiden (The Netherlands).

UNIVERSITY OF ILLINOIS

The Department of Otolaryngology, University of Illinois College of Medicine, will conduct a postgraduate course in Laryngology and Bronchoesophagology from October 23 through November 4, 1961, under the direction of Paul H. Holinger, M.D.

Registration will be limited to fifteen physicians who will receive instruction by means of animal demonstrations and practice in bronchoscopy and esophagoscopy, diagnostic and surgical clinics, as well as didactic lectures.

Interested registrants will please write directly to the Department of Otolaryngology, University of Illinois College of Medicine, 1853 West Polk Street, Chicago 12, Illinois.

AMERICAN BOARD OF OTOLARYNGOLOGY

The American Board of Otolaryngology will conduct only one examination in 1961, and this will be October 2-5, 1961, in Chicago, Illinois, at the Palmer House.

Dean M. Lierle, M.D., Secy.

ANNALS

In order to fulfill the requests for the March 1935, March 1937, March 1955, March 1956, December 1958, March 1959 and June 1959 issues, the ANNALS will pay \$3.50 for each book in good condition.

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AMERICAN LARYNGOLOGICAL, RHINOLOGICAL AND OTOLOGICAL SOCIETY, INC.

President: Dr. Theo. E. Walsh, St. Louis

Secretary: Dr. C. Stewart Nash, 708 Medical Arts Bldg., Rochester, N.Y.

Meeting: Sheraton-Dallas Hotel, Dallas, Tex., May 1-3, 1962

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Meeting: Sheraton-Dallas Hotel, Dallas, Tex., April 29-30, 1962

VII INTERNATIONAL CONGRESS OF OTOLARYNGOLOGY

President: Prof. M. Aubry, Paris

Sec. Gen.: Dr. H. Guillon, 6 Ave. Mac-Mahon, Paris XVII France

Meeting: Paris, July 15-22, 1961

INTERNATIONAL BRONCHOESOPHAGOLOGICAL SOCIETY

President: Dr. Giorgio Ferreri, Rome, Italy

Acting Secretary: Dr. Charles M. Norris, 3401 N. Broad St., Philadelphia 40, Pennsylvania, U.S.A.

Meeting: 10th International Congress of Bronchoesophagology, Reims, France, and Düsseldorf, Germany, July 30 - August 2, 1961

PAN-AMERICAN ASSOCIATION OF OTO-RHINO-LARYNGOLOGY AND BRONCHO-ESOPHAGOLOGY

President: Dr. Plinio de Mattos Barretto, São Paulo, Brazil

Acting Executive Secretary: Dr. Charles M. Norris, 3401 N. Broad St., Philadelphia 40, Pennsylvania

Meeting: Eighth Pan-American Congress of Oto-Rhino-Laryngology and Broncho-Esophagology; President: Dr. Alfredo Celis Pérez, Valencia, Venezuela; February, 1962, Venezuela

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President: James E. Lett, Col. USAF MC

Secretary-Treasurer: Gerald W. Hurst, Capt. MC USN, U. S. Naval Hospital, Great Lakes, Illinois

Meeting: Chicago, Ill., October, 1961

